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Evaluating the consistency with guideline recommendations for diagnosis and management of idiopathic pulmonary fibrosis in non-academic settings

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Abstract. *Background:* Idiopathic pulmonary fibrosis (IPF) is a progressive lung disease with elevated mortality. Delay in diagnosis lead to worse outcomes. Guidelines developed at academic medical centers are difficult to replicate in the community. *Objectives:* Our primary objective was to ascertain consistency with the 2011 IPF guidelines. Our secondary objective was to conduct an interdisciplinary review to ascertain whether the evidence supported the original diagnosis of IPF or not. *Methods:* We asked permission from pulmonologists to review records of patients diagnosed with IPF after 2011. We collected physician demographics and training data; patient demographics, clinical and diagnostic/management data. The clinical data and available images were reviewed by the interdisciplinary review panel. *Results:* 26 practicing pulmonologists located in the Southeast of the United States consented to participate. Mean age was 48, 70% were male and all had current certification. We reviewed data from 96 patients. The mean age was 71.4 and most were male. Only 23% had the recommended screening for a connective tissue disease and 42.6% were screened for exercise-induced hypoxemia. Among patients with available images for review (n=66), only 50% had a high-resolution CT scan. 22% of patients underwent a surgical biopsy and in only 33% of the cases three lobes were sampled. No patient had documentation that a multidisciplinary discussion occurred. In 20% of the cases with available images, the evidence supported an alternative diagnosis. 56% of eligible candidates were ever started on anti-fibrotics. *Conclusions:* Our findings suggest that consistency with the IPF guidelines is low in non-academic settings.

Key words: idiopathic pulmonary fibrosis, diagnosis, adherence to guidelines

Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a relentlessly progressive chronic fibrosing lung disease with a median survival of only 3-5 years from the time of diagnosis. Delays in diagnosis are common and may lead to worse outcomes (1, 2). IPF is not curable but two approved antifibrotic drugs have been shown to

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reduce the rate of disease progression in well-characterized cohorts (3, 4). Furthermore, recently identified targets are being tested in ongoing and future clinical trials (5, 6). There is, therefore, an imperative for timely and accurate diagnosis of IPF from both clinical and research perspectives (7).

The diagnosis of IPF requires careful appraisal of clinical data, imaging, and lung histology. A technically adequate high-resolution CT scan of the chest (HRCT) interpreted by a thoracic radiologist is the diagnostic algorithm centerpiece and often abrogates the need for a biopsy. When deemed necessary, biopsies ought to be performed by an experienced surgeon and interpreted by a lung pathologist. The 2011 ATS/ERS/JRS/ALAT guidelines (henceforth referred to as "the guidelines") added the recommendation that a multidisciplinary team with clinicians, thoracic radiologists, and lung pathologists be assembled to establish diagnosis, particularly for patients sent for a lung biopsy. Additionally, the guidelines also contain recommendations for post-diagnosis management that includes 1) clinical assessment with pulmonary function testing (PFT) every 4 to 6 months; 2) oxygen therapy if hypoxemia is present; 3) referral to pulmonary rehabilitation; and 4) lung transplantation for appropriate patients (8) . The 2011 guidelines were updated in 2015 to include a "conditional recommendation" for use of the anti-fibrotic drugs nintedanib and pirfenidone in the majority of the patients with IPF (9). The 2018 ATS/ERS/JRS/ALAT guidelines updated the recommendations regarding the diagnostic process but did not address post diagnostic management strategies (10). The 2018 guidelines were updated in 2022 and recognized the value of the transbronchial cryobiopsy as an alternative to surgical lung biopsy (11).

Academic and community practitioners often disagree regarding the diagnosis of IPF and processes that are developed within academic medical centers to primarily inform research can be difficult to translate into clinical practice (12). In this study, our primary objective was to measure the consistency to follow the IPF guidelines in non-academic settings. Our secondary objective was to conduct an interdisciplinary review of cases to assess whether the available evidence supported the original diagnosis of IPF or not.

Materials and Methods

The University of Alabama at Birmingham (UAB) Institutional Review Board for Human Research (IRB) reviewed and approved this study. Our study subjects were practicing non-academic pulmonologists in the States of Alabama, Georgia, Mississippi, and Florida that are registered with the UAB Department of Continuing Medical Education (n=122). We contacted individuals via email and/or telephone and 26 pulmonologists consented to participate. We asked each pulmonologist to identify up to ten patients that they had personally diagnosed with IPF and managed at least six months after the publication of the 2011 guidelines. To avoid skewing the results, no more than five pulmonologists from any given practice could participate and, no pulmonologist could contribute more than 10 cases. We excluded those practicing in an academic setting or in a site of the Pulmonary Fibrosis Foundation Clinical Care Network. A research coordinator traveled to each office and obtained demographic and training information from each pulmonologist, de-identified patient demographics, and data on clinical characteristics, diagnostic procedures, and post-diagnosis management. The research coordinator also procured de-identified CDs with all the available chest images, and reports of surgical lung biopsies, when applicable. We did not obtain the slides of the surgical biopsies. Each case was jointly reviewed and classified at UAB by an experienced interdisciplinary review panel that had worked together in weekly ILD conferences for over 10 years. The Radiologist reviewed each available Computed Tomography (CT) scan in detail to determine the technique (HRCT, CT angiogram, or regular CT scan) according to practice parameters (13) and to assign a "most likely pattern" (Usual Interstitial Pneumonia [UIP], Probable UIP, Indeterminate, or consistent with a diagnosis other than UIP) according to contemporary guidelines (10, 14).

The review panel was biased in favor of the original diagnosis and the primary task was to evaluate the quality of the evidence that was available to the community pulmonologist rather than issuing a specific diagnosis. For each case the reviewers considered the following questions: 1) "*Assuming that a comprehensive history and physical examination was performed, did the*

pulmonologist caring for this patient had enough evidence to issue a diagnosis?" and *"If there was enough evidence, are there features that support a diagnosis other than IPF?"*. Each case was then classified as follows: 1) Evidence supports IPF; 2) Evidence supports alternative diagnosis; 3) Indeterminate – the analysis of the available data (including imaging) did not allow for a confident adjudication either way. 4) Unable to adjudicate because imaging was not available for review.

Statistical Analysis

Descriptive statistics of the characteristics of physicians and patients are presented as means and standard deviations of the continuous variables and frequency and proportions of the categorical variables. We compared physician's and patient's characteristics by adjudication results using Fisher's exact test and ANOVA as appropriate. A Kruskal-Wallis test was performed as a non-parametric test of ANOVA(15). All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA) with significance level set at α=0.05.

Results

Physician characteristics

From the list of 122 pulmonologists, 26 agreed to participate and provided informed consent. The mean age was 48 years, and the majority (70%) were male. All had a current certification from the American Board of Internal Medicine in Pulmonary Disease and the average time since graduation from subspecialty training was 14.8 years. Although the majority trained in a program that had a specialized ILD center (58%) and/or a lung transplantation center (69%) (Table 5), no one had specific and individual training in either ILD or lung transplantation.

Patient demographics and clinical characteristics

The 26 pulmonologists contributed 96 patients for the medical record review phase. Most patients were Caucasian males and the physiological profile was comparable to that of IPF cohorts recently reported (3, 4) (16). Cough was the most common chief complaint and the mean duration of symptoms prior to diagnosis was 10 months (Table 1).

Diagnostic process

All patients had had some form of chest imaging and we had access to all the reports but 31% did not have images available for review. This was due to unavailability of digital versions of hard copies that had been long destroyed. Among those with available images (n=66), approximately 50% had a good quality HRCT and the others had been diagnosed based on a CT angiogram or a regular, thick-sliced, CT of the chest. Only 18% of the radiology reports were issued using the recommended contemporaneous nomenclature. 22% of the overall cohort underwent a surgical lung biopsy. Among these, less than one third had samples obtained from three different lobes. The minimal connective tissue disease serological evaluation recommended (Anti-Nuclear Antibody [ANA], Rheumatoid Factor [RF], Anti-Cyclic Citrullinated Peptide [CCP]) was completed in only 23% and less than half of the patients were screened for exercise-induced hypoxemia (Table 2). All patients had resting oximetry values available for review. 25% of all patients were referred for a confirmatory consultation at some point during their disease trajectory.

Post diagnostic follow up

The majority of patients fulfilled the guidelines' recommendations for the number of clinic visits but only a minority had follow-up pulmonary function tests, referrals to pulmonary rehabilitation, and screening for exercise-induced hypoxemia. Only 35% of age-eligible patients were referred to a lung transplant center and only 56% of those patients diagnosed after the anti-fibrotic drugs became commercially available were ever started on either nintedanib or pirfenidone (Table 3).

Interdisciplinary Review of the Clinical Evidence

Although only half of the available CT scans were performed with a high-resolution protocol, the

Table 1: Patients characteristics and clinical data at the time of diagnosis (*) (n=96)		
Age in years		71.4 (9.8)
Gender (% female)		44.8
Race (% Caucasian)		81.3
Duration of symptoms prior to diagnosis, months		10 (22.4)
Chief Complaint (%)	Cough	43.8
	Dyspnea	29.2
	Chest Pain	3.1
	Other	24
Co-morbidities (%)	Gastroesophageal Reflux	47.9
	Coronary Artery Disease	28.1
	Diabetes	25
	Obstructive Sleep Apnea	22.9
	COPD	18.8
	Pulmonary Hypertension	2.1
BMI		29.1 (5.7)
Family history of pulmonary fibrosis (%)		7.3
FVC, L		2.3 (0.8)
FVC % predicted		64.2 (14.7)
DLCO, mL/min/mmHg		10 (3.7)
DLCO % predicted		44.6 (15.3)
Hypoxemia at rest (%)		10.3
(*) Data are mean (SD) unless otherwise noted		

Table 2: Diagnostic process (*)		
CT technique	HRCT	33
	Regular CT	19
	CT angiogram	17
	Images not available	31
ANA, RF, CCP measured (**)		22.9
Bronchoscopy with bronchoalveolar lavage		14.6
Bronchoscopy with transbronchial biopsy		6.3
Surgical lung biopsy (n=21)		21.9
Number of lobes sampled	One	6/21
	Two	6/21
	Three	6/21
Performed at local hospital		18/21
Report by local pathologist		11/21
Multidisciplinary discussion		0
Oxygen saturation measured at rest		100
Oxygen saturation measured during exertion		41.7
(*) Data are % unless otherwise noted; (**) ANA: anti-nuclear antibody; RF: rheumatoid factor; CCP: anti cyclic citrullinated antibody		

Table 3: Post diagnosis management (*)	
Completed expected number of clinic visits	
Completed expected number of PFTs	
Completed expected number of referrals to pulmonary rehabilitation (**)	
Referred to a lung transplant center (if age ≤ 65)	34.6
Referred for a confirmatory consultation or second opinion	25
Started on either nintedanib or pirfenidone (***)	55.9
(*) Data are % unless otherwise noted; (**) Considered "completed" if at least one referral/year of follow up occurred; (***) if drugs were available	

study Radiologist assigned a "most likely pattern" to all studies according to current guidelines (10, 14). 47% of all reviewed scans had a "most likely pattern" of UIP or Probable UIP (Table 4). We did not have access to the biopsy slides but 14 out of 21 surgical lung biopsies had detailed written reports available for review and the majority (n=9) had a UIP pattern. The review panel was unable to classify 31% of the patients because images were not available. 66 images were available for review. The review panel concluded that the evidence available suggested a diagnosis other than IPF in 20% and 13.5% of the cases with available images and the entire cohort, respectively (n=13, Table 4). When comparing the three groups by classification result, there were no differences in physician's characteristics, but those patients classified as "Evidence supports alternative diagnosis" (n=13) were younger, more likely to be female, and all had a CT pattern "consistent with a diagnosis other than UIP" (Table 6). Six patients whose surgical lung biopsies were reported as UIP also had Chest CT scans available for review and all had a pattern different than UIP.

Discussion

The recommended diagnostic process for IPF is based on an algorithm that requires integration of clinical, serological, radiographic, and sometimes histological data by a multidisciplinary team. Delays can be associated with worse outcomes but it is important to remember that a diagnosis of IPF should

Table 4: Interdisciplinary review		
Analysis of imaging technique	HRCT	33.3
	Regular CT	18.8
	CTA	16.7
	Images not available	31.3
Most likely pattern of available CT scans (n =66)	Other than UIP	39.4
	Probable UIP	30.3
	UIP	16.7
	Indeterminate	13.6
Surgical Lung Biopsy (n=21) – report review in absolute numbers	Report not available	7
	Alternative Diagnosis	2
	Probable UIP	3
	UIP	9
Classification (n=96)	Evidence supports IPF	30.2
	Indeterminate	25
	Evidence supports alternative diagnosis	13.5
	Unable to adjudicate – missing CT scan	31.3
(*) Data are % unless otherwise noted.		

Table 5: Physician demographics and information (*)	
Age in years	47.9 (9.27)
Gender (%female)	30.2
Years since graduation	14.8 (8.8)
Board Certification current (%)	100
Trained with ILD Program (%)	58.3
Trained with Lung Transplant Program (%)	68.8
(*) Data are mean (SD) unless otherwise noted	

not be issued lightly given its poor prognosis (2). Furthermore, a specific diagnosis also has treatment implications as the anti-fibrotic drugs are, at this time, only approved for specific populations (17). Similarly, clinical trials exploring novel therapies include only patients with typical findings and high degree of diagnostic certainty. It is highly desirable, therefore, that the recommended processes for the diagnosis and management of IPF are followed in an accurate and timely manner.

Our study is the first to directly survey the records of IPF patients diagnosed by pulmonologists in non-academic settings with the primary objective to determine the consistency of their practices with guideline recommendations. Our observations demonstrate that: (1) only a minority of patients had a complete clinical investigation; (2) the suggested HRCT chest imaging technique was followed in only one half of cases; (3) when a surgical biopsy was performed, three lobes were sampled in only one third of the cases; (4) no one was diagnosed via a multidisciplinary discussion. In the post diagnosis management period, there was good adherence to the recommended number of follow-up clinic visits but less so regarding follow-up PFTs, pulmonary rehabilitation referrals, and prescription of the approved anti-fibrotic drugs.

One strength of our study is the fact that we conducted a systematic interdisciplinary review of each case. It considered first whether there was enough evidence to allow for a diagnosis with a reasonable amount of certainty and, if so, whether there were any features in the clinical, imaging, or serological data that supported a diagnosis other than IPF. 38.5% of the cases had either evidence that supported a diagnosis other than IPF or lacked sufficient data, suggesting that non-academic pulmonologists may have a low diagnostic threshold. This finding is similar to what was reported by Flaherty and colleagues (12). They sequentially presented clinical data, lung function, imaging, and histology from 39 patients with interstitial lung disease (ILD) to academic and community physicians. As the participants reviewed more data and, as interaction between clinicians, radiologists, and pathologists increased, interobserver agreement improved for both groups but it was better among those

Table 6: Characteristic of patients according to adjudicated diagnosis (*)

Variable	Evidence Supports IPF (n = 29)	Indeterminate (n = 24)	Evidence Supports Alternative Diagnosis (n =13)	p value
Age of treating MD	47 (10.4)	48.2 (9.6)	53 (10.4)	0.21
Treating MD - years in practice	13.9 (10.2)	14.2 (8.6)	19.6 (10.3)	0.18
Treating MD - ILD training (%)	58.6	58.3	53.8	0.95
Treating MD - Transplant training (%)	72.4	66.6	38.4	0.09
Age of patient	73.2 (7.3)	73.3 (9.5)	65 (13.3)	0.02
Gender (% female)	24.1	50	61.5	0.04
Race (% Caucasian)	89.6	83.3	76.9	0.50
FVC % predicted	64.7 (12.8)	65.5 (14.1)	68.2 (22.3)	0.80
DLCO % predicted	46.3 (17.7)	48.1 (13.6)	41.4 (14.5)	0.60
CT pattern (%)				
UIP	31	8.3	0	<0.0001
Probable UIP	51.7	21	0	
Indeterminate	7	29.1	0	
Other than UIP	10.3	41.6	100	
Hypoxemia at rest? (%)	3.8	21.7	9.09	0.12
(*) Data are in means (SD) unless otherwise noted				

in academic centers. There was significant disagreement between academic and community physicians and a final diagnosis of IPF was more likely to be assigned by community physicians.

The fact that a substantial number of patients might have been misclassified is significant. Some patients were told that they had a lethal disease when they probably did not. Furthermore, many patients were not receiving the potential benefits of anti-fibrotic therapy or a timely lung transplant referral.

The fact that we obtained data from medical records makes it difficult to compare our findings with those of surveys of pulmonologists. Peikert and colleagues conducted a survey of the Fellows of the American College of Chest Physicians to measure acceptance and implementation of the 2000 ATS/ERS IPF guidelines. The majority (72%) declared familiarity with the guidelines and 63% found them to be useful. 86% declared that they refer patients to lung transplant centers (18). In contrast, we found that only 35% of age eligible IPF patients were referred to a lung transplant center. It is possible that the discrepancy stems from a response bias rooted in the belief by the responders that referring an IPF patient to a lung transplant center is the right thing to do, whereas our study measured real-world practice. We recognize that the decision to refer an individual patient for lung transplant evaluation takes into consideration many more variables than age alone and is often based on personal preferences and the presence of co-morbidities. Ascertaining whether the number of lung transplant referrals was appropriate is beyond the scope of this manuscript.

European registries that enrolled patients diagnosed and managed in specialized centers report that a diagnostic MDD was conducted in up to one third of the cases, which exceeds what we observed in our study (19, 20). Pulmonologists practicing away from specialized centers report lower access to experienced radiologists and pathologists and we suspect that those participating in our study faced similar challenges (20).

Low adherence to evidence-based practices and guidelines is not unique to IPF. Starfield and colleagues conducted a chart review of Medicaid claims data in the U.S. On average, 40 to 45% of technical quality indicators that were based on contemporaneous evidence-based practices were not met in a cohort of stable chronic asthmatics (21). In fact, a subsequent survey of the literature exploring the quality of medical care in the U.S. suggests that a substantial portion of the population either does not receive evidence-based care or actually receives care that is contraindicated (22).

Physicians have many barriers to guideline adherence and several reports have attempted to characterize those. Cabana and colleagues identified seven categories of barriers: 1) lack of awareness; 2) lack of familiarity; 3) lack of agreement; 4) lack of self-efficacy (physicians do not believe they can perform the recommendations); 5) lack of outcome expectation (physicians do not believe adherence to guidelines will lead to the desired outcome); 6) inertia of previous practices; and 7) external barriers such as lack of time, lack of resources, organizational constraints, lack of reimbursement incentive (23). Cochrane and colleagues conducted a systematic review of the English language literature and identified seven broad categories of barriers: 1) cognitive-behavioral barriers (lack of knowledge, awareness, professional skill, or appraisal skills); 2) rational-emotional barriers (lack of efficacy, lack of confidence, lack of outcome expectancy, etc.); 3) professional barriers (age, experience, lack of motivation, lack or peer influences, etc.); 4) barriers embedded in the guidelines (lack of practical access, lack of comprehensible structure, lack of local applicability, lack of convincing evidence, etc.); 5) patient barriers; 6) resources (lack of time, lack of human and material resources, etc.); and 7) system and process barriers (lack of organization and structure, lack of referral process, lack of workload-outcome balance, lack of teamwork structure) (24).

In the specific case of IPF, there are several aspects of the patient diagnostic investigation and management that are fully under the control of the pulmonologist such as ordering the correct imaging and serological evaluation, screening for hypoxemia, and obtaining follow up pulmonary function testing. Future studies should focus on understanding the reasons behind the inconsistencies that we found. Additionally, barriers related to systems and resources such as time constraints, lack of access to expertise

in radiology and pathology, overall low quality of the evidence, lack of financial incentive and unavailability of a pulmonary rehabilitation program are all likely culprits preventing the full implementation of the guidelines in the community (25-27).

Our study has several limitations. First, it sampled only approximately 20% of the pulmonologists registered with our institution CME Department. Those who agreed to participate might have had a stronger interest in IPF, thereby introducing a systematic bias. Our study is limited to one area in the U.S., whose population and socioeconomic status may not be representative of the entire country. In fact, previously reported geographic differences in IPF outcomes furthers the concern that the limitations found in the clinical evaluation of patients with possible IPF by this cohort of physicians may be specific to the region and may not represent practice throughout the United States (28). Approximately one third of the cases could not be fully ascertained because the images were not available, which could have led to an underestimation of potential cases of misdiagnosis. Additionally, we did not have access to the slides of the 21 cases in which a surgical lung biopsy was performed. Considering these limitations, the interdisciplinary review panel had to take a conservative approach, and the original diagnosis was affirmed unless the evidence was overwhelmingly against it. Also, other important aspects of post diagnosis management such as screening for sleep-disordered breathing, referral to palliative medicine, symptom management, and safety monitoring of anti-fibrotics were not addressed.

Conclusion

Our findings suggest that consistency with the main tenets of the IPF guidelines is low in non-academic settings. We also demonstrate that several patients were potentially misdiagnosed. The barriers faced by those practicing in non-academic settings are likely multifactorial and difficult to overcome. Future guideline development ought to consider the "implementability" of its recommendations and, in the meantime, patients suspected of having IPF should, whenever possible, be evaluated in specialized ILD centers for diagnostic confirmation and development of a management plan.

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