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Pulmonary function testing for fitness assessment in asymptomatic adults with newly diagnosed acute myeloid leukemia

Running Head: Pulmonary Function Testing in Adults with AML

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TO THE EDITOR

Intensive multiagent chemotherapy has been a cornerstone of curative-intent treatment for adults with acute myeloid leukemia (AML) for several decades.[1, 2] More recently, the market introduction of several new drugs has expanded the therapeutic options for such patients.[3-5] With increasingly diverse treatments available, there is growing interest in instruments that assess medical fitness to aid the selection of the most suitable therapeutic strategy for individual patients. Now widely used for this purpose are criteria proposed by investigators from the Italian Society of Hematology (SIE), the Italian Society of Experimental Hematology (SIES), and the Italian Group for Bone Marrow Transplantation (GITMO).[6] We recently reported in 703 adults with AML or other high-grade myeloid neoplasm that these "Ferrara" criteria are indeed useful for patient risk-stratification and have a good to very good accuracy for the prediction of shorter-term mortality following intensive AML chemotherapy.[7]

Our data indicated the importance of pulmonary assessments to categorize patients as fit or unfit for intensive AML chemotherapy as pulmonary abnormalities were the single most common reason for medical unfitness based on Ferrara criteria.[7] However, this fitness evaluation requires lung function testing, which is not routinely performed in many institutions and may be perceived as an unnecessary burden for asymptomatic patients. For example, in our cohort, only 159 of the 703 patients underwent pulmonary function testing before chemotherapy initiation. Some of our analyses suggested that the absence of known pulmonary comorbidities combined with the lack of respiratory symptoms could serve as a surrogate for normal pulmonary function, thereby avoiding the need for formal testing.[7] To test this idea, we analyzed a cohort of adults ≥18 years of age with previously untreated AML (2016 WHO criteria[8]) who were admitted to the Hematology Unit of the Policlinico Tor Vergata (Rome, Italy) between 01/2009 and 12/2020 and underwent pulmonary function testing as routine part of the pre-treatment assessment. This retrospective analysis was approved by the Fred Hutchinson Cancer Center and Policlinico Tor Vergata Institutional Review Board.

Information on pulmonary function testing, chest radiographs, smoking status, and prior/concurrent pulmonary comorbidities was collected from medical records. Patients were classified as pulmonary unfit according to Ferrara criteria (F-unfit) in case of abnormal lung function testing with diffusing capacity for carbon monoxide (DLCO) ≤65% predicted (relative to accepted reference values) or forced expiratory volume in the first second (FEV1) ≤65% predicted, dyspnea at rest, need for supplemental oxygen, or history of any pleural neoplasm or uncontrolled lung neoplasm.[6] Chest imaging reports were reviewed by one of the authors (R.P.) and categorized as "normal" (no radiological abnormalities reported), "new"

(previously unknown abnormalities reported), “stable” (previously known abnormalities reported to be unchanged), “changed” (previously known abnormalities reported to be changed), and “increased” or “decreased” (worsening or improvement of previously known abnormalities).

Two hundred forty-three patients met our study inclusion criteria. As summarized in **Table 1**, current and former smokers accounted for a minority of patients in these cohorts. Pulmonary comorbidities were identified in 14/243 (6%) of the patients. Chest imaging studies were available in all cases and were normal in 120/243 (49%) of the patients. Forty-five of the 243 patients (19%) had dyspnea at rest requiring oxygen. Less than 20% (38/243 [16%]) had normal pulmonary function testing results (*i.e.* DLCO and FEV1 ≥91%). In contrast, in 47 (19%) of the patients, pulmonary function was severely abnormal (*i.e.* FEV1 and/or DLCO ≤65%), establishing pulmonary unfitness according to the criteria proposed by Ferrara and colleagues.[6]

Of the 243 patients, 59 (24%) met criteria for pulmonary Ferrara (F-)unfitness. Isolated pulmonary function test abnormalities were the reason for F-unfitness in only 12/59 (20%) of the patients, with isolated dyspnea (n=11 [19%]), active lung cancer (n=1 [2%]), and the combination of abnormal lung function tests together with dyspnea at rest (n=34 [58%]) or active lung cancer (n=1 [2%]) accounting for the remaining cases.

Because of our recent data suggesting the absence of F-unfitness-defining pulmonary comorbidities and lack of respiratory symptoms (i.e. dyspnea at rest or requiring supplemental oxygen, or any pleural neoplasm or uncontrolled lung neoplasm) could potentially serve as a surrogate for normal pulmonary function,[7] we were particularly interested in the patients without pulmonary symptoms and no history of F-unfitness-defining pulmonary disease. Among the 243 patients, 196 (81%) met these characteristics (**Supplemental Table 1**). Of these 196 individuals, pulmonary function testing was severely abnormal (*i.e.* denoting F-unfitness) in 12 (6%) of patients. In this small subset of patients with severely abnormal pulmonary function tests, 7 (58%) had abnormal radiographic findings, the majority of which (6/7 [85%]) were increased or new. Furthermore, 5/12 (42%) of these patients had lung comorbidities that were documented but did not qualify for F-unfitness on their own, including obstructive pulmonary diseases (n=4) and prior lobectomy (n=1). Finally, current/prior smokers accounted for over half of these patients (8/12 [67%]). As one might expect, the likelihood of severely abnormal lung function differed across individual patient subsets depending on past/current smoking status, presence of pulmonary comorbidities, and chest imaging findings (**Table 2**). Among life-long non-smokers without

known pulmonary comorbidities and normal chest imaging studies – the largest subset of patients, overall accounting for 78/196 (40%) of the patients – lung function studies were severely abnormal in only 2 (1%) of the patients. On the other hand, among the 7 past/current smokers with known pulmonary comorbidities and abnormal chest imaging findings, lung function studies were severely abnormal in 5 (71%) of the patients (**Supplemental Figure 1**).

Together, in the cohort of adults with previously untreated AML we studied, the vast majority of patients neither had respiratory symptoms nor pulmonary comorbidities that would qualify for unfitness based on Ferrara criteria.[6] Thus, the question of whether the absence of pulmonary symptoms and lack of pulmonary comorbidities could serve as a surrogate for normal pulmonary function for the purpose of Ferrara fitness assessment is clinically relevant as pulmonary function testing is not routinely performed in many centers treating AML. Our data show that the lack of respiratory symptoms together with lack of pulmonary comorbidities is not indicative of having normal pulmonary function tests. In fact, they were normal in less than 20% of such patients, and mildly or moderately abnormal test results were common. Moreover, across all patients, severely abnormal pulmonary function tests were found in almost 20% of cases. However, our findings indicate that among non-smokers with normal chest imaging studies and no history of pulmonary comorbidities, severely abnormal pulmonary function tests were uncommon. In our cohort, only 1% of such patients had a severely abnormal lung function. In other words, for patients meeting these characteristics, about 100 pulmonary function testing studies would need to be done to identify one patient with findings abnormal enough to qualify for Ferrara unfitness. Thus, in such patients, it would appear reasonable to forgo pulmonary function testing if only done for the purpose of Ferrara fitness assessment using current criteria.

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TABLE 1. Characteristics of study population

	All patients (n=243)
Median age (range), years	64.9 (22.4-88)
Female gender, n (%)	102 (42%)
Smoking status, n (%)	
Current	36 (15%)
Past	59 (24%)
Chest imaging available, n (%)	243 (100%)
X-rays	19 (8%)
CT scan	223 (92%)
PET-CT	1 (<1%)
Imaging findings, n (%)	
Normal	120 (49%)
Stable	29 (12%)
New	44 (18%)
Increased	28 (12%)
Decreased	22 (9%)
Documented lung comorbidity, n (%)	14 (6%)
Active lung cancer	1 (<1%)
Obstructive pulmonary disease	11 (5%)
Fungal pneumonia	0
OSAS	0
Prior lobectomy	1 (<1%)
Tuberculosis	1 (<1%)
Asbestosis	0
Interstitial lung disease	0
Supplemental oxygen use, n (%)	
During day	45 (19%)
At night (CPAP)	0
None	198 (82%)
Pulmonary Ferrara score, n (%)	
Fit	184 (76%)
Unfit	59 (24%)
PFT	*12 (20%)*
Dyspnea	*11 (19%)*
Dyspnea and PFT	*34 (58%)*
Active lung cancer	*1 (2%)*
PFT and active lung cancer	*1 (2%)*

TABLE 2. Results from pulmonary function testing across different subsets of patients who had no pulmonary symptoms and lacked F-unfitness-defining pulmonary comorbidities (196 patients)

	Pulmonary Function			
	Normal*	Mildly abnormal**	Moderately abnormal***	Severely abnormal****
Non-smoker, no pulmonary comorbidities, normal chest imaging (n=78)	19 (24%)	28 (36%)	29 (37%)	2 (3%)
Smoker, no pulmonary comorbidities, normal chest imaging (n=36)	7 (19%)	14 (39%)	12 (33%)	3 (8%)
Non-smoker, pulmonary comorbidities, normal chest imaging (n=0)	0	0	0	0
Non-smoker, no pulmonary comorbidities, abnormal chest imaging (n=42)	8 (19%)	11 (26%)	21 (50%)	2 (5%)
Smoker, pulmonary comorbidities, normal chest imaging (n=0)	0	0	0	0
Smoker, no pulmonary comorbidities, abnormal chest imaging (n=31)	4 (13%)	11 (36%)	16 (52%)	0
Non-smoker, pulmonary comorbidities, abnormal chest imaging (n=2)	0	0	2 (100%)	0
Smoker, pulmonary comorbidities, abnormal chest imaging (n=7)	0	1 (14%)	1 (14%)	5 (71%)
All patients (n=196)	38 (19%)	65 (33%)	81 (41%)	12 (6%)

*DLCO and FEV1 ≥91%; **DLCO and/or FEV1 81-90%; ***DLCO and/or FEV1 66-80%; ****DLCO and/or FEV1 ≤65%

TABLE 1S. Characteristics of 196 patients who had no pulmonary symptoms and lacked Ferrara unfitness-defining pulmonary comorbidities.

	Number (%) [Total=196]
Female gender	83 (42%)
Smoking history	74 (38%)
Pulmonary function testing	
*Normal**	38 (19%)
*Mildly abnormal***	65 (33%)
*Moderately abnormal****	81 (41%)
*Severely abnormal*****	12 (6%)
Chest imaging	
Normal	114 (58%)
Stable	26 (13%)
New	31 (16%)
Increased	1 (<1%)
Decreased	21 (11%)
Documented lung disease[$]	8 (4%)
Ferrara score pulmonary	
Fit	184 (94%)
Unfit	12 (6%)

*DLCO and FEV1 ≥91%; **DLCO and/or FEV1 81-90%; ***DLCO and/or FEV1 66-80%; ****DLCO and/or FEV1 ≤65%

[$]Comorbidities not qualifying for Ferrara unfitness per se.

Pulmonary Ferrara criteria denoting patient to be “unfit”: DLCO and/or FEV1 ≤65%, dyspnea at rest, need for supplemental oxygen, or history of any pleural neoplasm or uncontrolled lung neoplasm.

FIGURE 1S. Study cohort distribution according to PFTs status, pulmonary comorbidities and chest imaging findings.