ORIGINAL RESEARCH

Clinical Impact of Multidisciplinary Outpatient Care on Outcomes of Patients with COPD

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Purpose: Heterogeneous nature of Chronic Obstructive Pulmonary Disease (COPD) must be comprehensively addressed. It is unclear if integrative multidisciplinary disease management (IMDM) can optimize clinical outcomes of patients with COPD.

Methods: A single-center, retrospective cohort observational study with a historical intervention was conducted in a clinic specialized for COPD care. Patients with a confirmed diagnosis of COPD were administered IMDM with measurement of BODE score on initial and follow-up visits. Primary outcomes were dynamic changes in BODE quartiles after receiving IMDM.

Results: Of 124 patients, 21% were misdiagnosed with COPD. Patients with a confirmed diagnosis of COPD were 50% female, median age 64 years (IQR 57–70), 43% actively smoking and initial visit median BODE quartile 2 (IQR 1–3). Three subgroups were identified based on the changes in BODE quartiles: worsened (21%), unchanged (55%) and improved (24%). At baseline, mMRC (median [IQR]) was higher in improved subgroup vs worsened and unchanged subgroup (3 [3, 4] vs 2 [1, 2] vs 2 [1, 3], p value 0.002) respectively. Drop in all components of BODE score was noted in worsened group, but significant improvement in mMRC with preservation of spirometry values was noted in the improved group. The incidence of smoking cigarettes changed from 39% to 26% during follow-up.

Conclusion: Our study demonstrates that IMDM can be potentially effective in a subgroup of COPD patients. In others precipitous drop in lung function, activity tolerance, and subjective symptoms seems inevitable with worsening BODE quartiles.

Keywords: BODE, integrative multidisciplinary disease management, clinical outcome, outpatient care

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death in the United States.[1,2] Of the five leading causes of death, COPD is the only disease with increasing mortality and health care cost.[1,2] Significant economic and healthcare burden due to COPD have led to a number of initiatives to improve COPD-associated outcomes and to reduce healthcare expenditure. However, complexity associated with pathology, diagnosis, and treatment of COPD has hampered optimal management of patients with COPD in outpatient clinic settings.

Two of the most challenging aspects in caring for COPD patients are to establish an accurate diagnosis of COPD and to manage complex physiologic derangement associated with COPD.[3–8] Even though Global Obstructive Lung Disease initiative (GOLD) has established irreversible airflow limitation measured by spirometry as

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a minimal diagnostic criterion, diagnosis of COPD is still made inconsistently.[9,10] Only 30–60% of smokers develop COPD, and sporadic use of spirometry has shown to cause highly prevalent misdiagnosis of COPD, thus, leading to inappropriate and ineffective therapeutic interventions.[2,11] As COPD becomes more severe, a number of pathologic derangements start to contribute to mortality that are not reflected by forced expiratory volume in 1 s (FEV_1) alone.[12–16] BODE index, composed of four clinically relevant and modifiable variables, body mass index (BMI), FEV_1, modified medical research council (mMRC) dyspnea scale, and 6 min walk distance (6MWD), has been shown to predict survival of patients with COPD by capturing complex pathophysiology.[17,18] Severity of symptoms has been found to be weakly correlating with airflow limitation, and two distinctive clinical subphenotypes of patients with COPD, ones experiencing frequent exacerbation and severe symptoms vs others with infrequent exacerbations and less symptom, have been appreciated in recent GOLD statements.[19] These findings are clearly in line with the fact that the activity tolerance and subjective symptomatology reflect the pathology of COPD that is not easily captured by spirometry alone. Exercise capacity reflects respiratory and systemic manifestations of COPD, with decline in 6MWD reflecting worsening physical function.[20,21] The mMRC score has been shown to have a clear relationship with health status impairment.[22] In line with this realization, the latest GOLD guidelines added the COPD Assessment Test (CAT) and mMRC to calculate the severity of COPD.[19]

Building upon this development, it is clear that administration of pharmacologic agents alone is grossly inadequate to treat patients with COPD. Instead a number of non-pharmacologic interventions are required to complement pharmacologic options. Unfortunately, administering comprehensive pharmacologic and non-pharmacologic interventions is time-consuming and requires substantial resources. This has led to integrated multidisciplinary disease management (IMDM) as a potential solution. Evaluating efficacy of IMDM has been limited due to lack of consensus definition of IMDM, lack of consistent application in various healthcare settings, and comparison made to "standard of care" without defining it.[23] Our study evaluates the impact of the comprehensive IMDM program at a tertiary care center by using dynamic changes in BODE score as a surrogate marker of therapeutic impact made by COPD-specific IMDM. We hypothesize that coordinated IMDM care improves clinically significant outcomes in patients with COPD.

Materials and Methods
Study Population and Method
A single-center, retrospective observational cohort study was conducted with patients referred to the University of Virginia (UVA) COPD clinic. This study was approved by institutional review board at the University of Virginia. All data used in this study were collected as a part of the outcomes measures which were determined under the Joint Commission Certification for the advanced COPD clinic. Performance outcomes data were collected as a part of a quality improvement project. Therefore, this protocol was considered an exempt protocol without need for consent. All patient data confidentiality was protected and in compliance with the declaration of Helsinki. These patients were referred with a pre-existing diagnosis of COPD. A diagnosis of COPD was established by GOLD criterion (post-bronchodilator $FEV_1/FVC<0.7$) according to the institutional standard clinical guideline which is in complete agreement with GOLD recommendations and with minor additional criteria unique to the UVA COPD clinic (Supplemental Figure 1). Patients who did not have at least one follow-up BODE score were excluded. Patients with a confirmed diagnosis of COPD during the initial and follow-up clinic visits were administered IMDM corresponding to treatments based on GOLD A-D classifications (Supplemental Figure 1). The IMDM team and interventions consisted of evaluation and standard education by a physician, a dedicated COPD nurse, and a respiratory therapist, individualized selection of pharmacologic agents after assessing inhaler use technique and competency, determination of socio-economic status related to the individual ability to obtain pharmacologic and non-pharmacologic care, social service intervention for financial and emotional support, and other standardized intervention based on COPD clinic protocol (mandatory referral to pulmonary rehabilitation and smoking cessation programs). During the follow-up visits, compliance to treatment, smoking status, inhaler technique, ability to access prescribed therapeutic interventions and competency of disease management were evaluated. Same IMDM was administered during the follow-up clinic visits to target the deficiencies as needed (Supplemental Figure 3).

Study Variables

Variables collected during the study were age, sex, smoking status, BMI, mMRC, 6MWD, BMI, Spirometry, treatment medications and duration between the initial and follow-up visits. To assess the change in BODE quartiles, consecutive BODE quartile assessment of each patient was performed during each visit. Assessment during the initial visit served as their baselines (V1=control) as compared to the assessments during the last visit to COPD clinic (V2=post IMDM). During V1 assessment all patients were using their inhalers according to the education they received from providers prior to the IMDM. Patients were specifically instructed to take their maintenance inhalers in the morning of the V2 visit in order to assess the therapeutic effects included in their management.

Statistical Analysis

Empirical frequencies and percentages were used to summarize nominal-scaled categorical patient characteristics and nominal-scaled categorical outcome metrics. The median and interquartile range (IQR) of the distribution were used to summarize all ordinal and continuous scaled patient characteristics and all ordinal and continuous scaled outcome metrics because the underlying distributions of the ordinal and continuous scaled patient characteristics could not reasonably be assumed to be Gaussian (i.e. Normal). With regard to hypothesis testing, nonparametric analytical method was used to test null hypotheses related to between-group comparisons and to test null hypotheses related to within-group comparisons. More specifically, the Mann–Whitney U-test was used to compare patient characteristics between patients with confirmed COPD diagnosis and misdiagnosed patients, as well as to compare patient characteristics between COPD patients with complete follow-up visits and patients without follow-up visits. The Wilcoxon Sign Rank test was used to compare BODE quartiles between initial and follow-up visits, and to compare V1 lung function and quality of life metrics to V2 lung function and quality of life metrics. The Kruskal–Wallis test was used to compare the V1 to V2 changes in lung function and quality of life metrics between 3 groups of subjects defined by changes in BODE quartiles (improved, worsened or unchanged). In terms of hypothesis test type I error rate control, only when the global null hypothesis for between-group differences was rejected based on the Kruskal–Wallis test, was the 2-sample Wilcoxon Rank Sum test was used to conducted pairwise between-group comparisons. Chi-square test was used to analyze any differences among groups regarding gender or smoking status. A two-sided $p \leq 0.05$ decision rule was used as the null hypothesis test rejection criterion for all global and pairwise between-group comparisons and a two-sided $p \leq 0.05$ decision rule was used as the null hypothesis test rejection criterion for all within-group comparisons.

Results
Baseline Characteristics of Patients with Misdiagnosis and Confirmed Diagnosis of COPD

One hundred and twenty-four patients were evaluated with a pre-existing diagnosis of COPD (Figure 1). Of
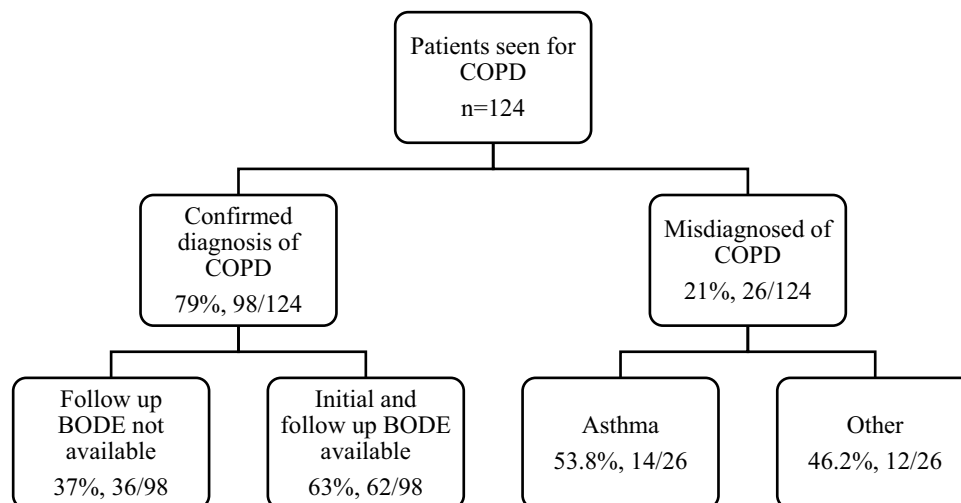
Figure 1 Study population section and numbers.

these patients, 26 patients (21%) were misdiagnosed with COPD. Alternative diagnoses were asthma, interstitial lung disease, congestive heart failure, physical conditioning or no lung disease identified (Figure 1). Baseline median FEV_1, median percent predicted FEV_1 (% FEV_1), median percent predicted FVC (%FVC), and median FEV_1/FVC ratios of the misdiagnosed patients were significantly higher as compared to patients with COPD (Table 1). Of 98 patients with a confirmed diagnosis of COPD, 50% were female, the median age was 63 yrs (IQR: [57, 70]) and 44% of COPD patients were actively smoking cigarettes at the time of initial visit (Table 1). Of the 98 patients with a confirmed diagnosis of COPD, initial and follow-up visit BODE scores were available for 62 (63%) COPD patients, but follow-up BODE scores were not available for 36 (37%) COPD patients – mostly due to being electively discharged back to the referring physicians with mild symptoms or patient preference (Figure 1). Baseline characteristics during the initial visit were not significantly different between COPD patients with and without follow-up visits. A lower percentage of females and a higher percentage of smokers were without follow-up, but the chi-square analysis showed no significant difference (Table 2). Baseline spirometry values were also comparable between these two groups of COPD patients. Similarly, median BODE quartile and numbers of patients in each quartile at the time of initial visit were comparable between these two groups of COPD patients (Table 2).

Characteristics of the Three Groups Defined by Changes in BODE Quartiles Before and After IMDM

Three subgroups of COPD patients (worsened, unchanged, and improved) were identified based on dynamic changes in BODE scores from the initial to follow-up visits; 21% with worse BODE quartile, 55% unchanged, and 24% improved (Table 3). These three groups had similar length of follow-up; median time between the initial and the last follow-up visits, worse (16.0, IQR: [9.5, 42.5]) vs unchanged (12.0, IQR: [6.0, 25.75]) vs improved (18.0, IQR: [5.0, 26.0]). The baseline demographics of these three groups at V1 are shown (Table 3). All baseline (IV) spirometry, 6MWD, and BMI were similar, but the median mMRC score was significantly higher in the improved groups as compared to the unchanged and worsened groups (median 3; IQR: [3, 4] vs median 2; IQR: [1, 3] vs median 2 IQR: [1, 2], respectively, *p=0.002*) (Table 3). The numbers of the subjects with clinically significant positive bronchodilator response per ATS criteria were similar among the three groups, 31% (worsened group), 26% (unchanged group) and 33% (improved group). Sixteen patients quit smoking from V1 (24 patients, 39%) to V2 (16 patients, 26%), but chi-square analysis showed no significant difference. A higher

Table 1 Confirmed COPD Patients vs Misdiagnosed

Total Patients (n)	COPD Patients (98)	Misdiagnosed COPD (26)	P value
Age (Median [IQR])	63 [57, 70]	64 [53, 74]	0.97
Sex			0.73
Male (%)	49 (50%)	14 (54%)	
Female (%)	49 (50%)	12 (46%)	
Active smoker (%)	43 (44%)	11 (42%)	0.89
Initial visit BODE quartile (Median [IQR])	2 [1, 3]	n.a.	
IV spirometry post BD (Median [IQR])			
FVC (Liter)	2.79 [1.97, 3.54]	3.02 [2.37, 3.74]	0.27
%FVC (% predicted)	78 [66, 89]	83 [75, 102]	0.017
FEV1 (Liter)	1.35 [0.93, 2.02]	2.23 [1.78, 2.87]	<0.001
%FEV1 (% predicted)	54 [39, 66]	87 [74, 98]	<0.001
FEV1/FVC	0.53 [0.42, 0.61]	0.76 [0.73, 0.80]	<0.001

Note: P value was generated by Mann–Whitney *U*-test.
Abbreviations: IQR, interquartile range; IV, initial visit; BD, bronchodilator; FVC, forced vital capacity; %FVC, percent predicted FVC; FEV1, Forced expiratory volume in 1 s; %FEV1, percent predicted FEV1.

Table 2 Demographics of COPD Patients

Total Patients (n = 98)	COPD Patients with Complete IV and FV (n = 62)	COPD Patients Without Complete IV and FO (n = 36)	P value
Age average (Median [IQR])	61 [55, 67]	66 [58, 71]	0.07
Sex			0.09
Male (%)	27 (44%)	22 (61%)	
Female (%)	35 (56%)	14 (39%)	
Active smoker (%)	24 (39%)	19 (53%)	0.18
IV BODE quartile (Median [IQR])	2 [1, 3]	2.5 [2, 3]	0.61
IV BODE quartiles			
First (%)	18 (29%)	8 (22%)	
Second (%)	14 (23%)	10 (28%)	
Third (%)	19 (31%)	10 (28%)	
Fourth (%)	11 (18%)	8 (22%)	
IV spirometry post-BD, (Median [IQR])			
FVC (Liter)	2.84 [2.05, 3.54]	2.74 [1.82, 3.62]	0.47
FVC (% predicted)	79 [71, 90]	75 [62, 87]	0.19
FEV_1(Liter)	1.40 [1.00, 2.00]	1.30 [0.83, 2.02]	0.81
FEV_1(% predicted)	54 [40, 66]	55 [38, 70]	0.89
FEV_1/FVC	0.52 [0.42, 0.59]	0.57 [0.40, 0.64]	0.49
6 MWD in meters (Median [IQR])	281 [227, 327]	249 [150, 316]	0.11
mMRC (Median [IQR])	2 [1, 3]	2 [1, 3]	0.95
BMI < 21 (%)	8 (13%)	2 (6%)	0.25

Note: P value was generated by Mann–Whitney U-test.
Abbreviations: IQR, interquartile range; IV, initial visit; BD, bronchodilator; FV, follow-up visit; FVC, Forced Vital Capacity; %FVC, percent predicted FVC; FEV1, forced expiratory volume in 1 s; %FEV1, percent predicted FEV1.

percentage of patients with worsened BODE quartiles quit smoking as compared to patients with unchanged or improved BODE quartiles, but chi-square analysis showed no significant difference.

Longitudinal Changes from Initial to Follow-Up Visits

Changes in spirometry were assessed by comparing the spirometry between V1 and V2. Significant reduction in absolute FVC was noted in all 3 groups (worsened: median $\Delta = -0.37$ L; 95% CI: [−0.71, −0.27], p=002, unchanged: median $\Delta = -0.27$ L; 95% CI: [−0.41,-0.09], p=<0.001, and improved: median $\Delta = -0.12$ L; 95% CI: [−0.31,-0.02], p=0.013) (Table 4, Figure 2). All other spirometry parameters were stably maintained in the improved group while the worsened and unchanged groups experienced significant declines in %FVC, absolute FEV, and %FEV1 (Table 4, Figure 2). Stepwise drops in 6MWD from V1 to V2 were noted with significant drop in the worsened group (median $\Delta = -53$ m, 95% CI: [−92, −7], p=0.012) as compared to minimal changes in the

unchanged group (median $\Delta = -1$ m, 95% CI: [−25, 50], p=0.92) and insginifcant increase in the improved group (median $\Delta = +43$ m, 95% CI: [−53, 67], p=0.23). Similar patterns of changes in mMRC from V1 to V2 were noted with significant increase in the wosened group (median $\Delta = +1$, 95% CI: [0, 1], p=0.031) as compared to unchanged (median $\Delta = 0$, 95% CI: [0, 0], p=0.48). However, mMRC was significantly reduced in the improved group (median $\Delta = -1$, 95% CI: [−1, 0], p=0.016) (Table 4, Figure 2).

Discussion

Our study has attempted to determine the therapeutic effects of IMDM on dynamic changes in BODE scores and components of BODE score for patients diagnosed with COPD. First, our study demonstrates that a significant percentage of patients who are referred for COPD actually do not have COPD. Second, of those with a confirmed diagnosis of COPD, three specific subgroups emerge depending on how their BODE score quartiles evolve after being intervened with IMDM. Third, patients

Table 3 Demographics on Initial Visit by Change in BODE Quartile

Bode Quartile (n)	Worsened (13)	Stable (34)	Improved (15)	P value
Age (Median [IQR])	57 [55, 71]	61 [57, 67]	60 [57, 71]	0.89
Sex				0.26
Male (%)	4 (31%)	18 (53%)	5 (33%)	
Female (%)	9 (69%)	16 (47%)	10 (67%)	
Active smoker (%)	7 (54%)	9 (26%)	8 (53%)	0.093
Medication				
SABA	12 (92%)	30 (86%)	14 (93%)	NA
SAMA	1 (8%)	8 (23%)	5 (33%)	NA
LABA	6 (46%)	22 (63%)	10 (67%)	0.45
LAMA	9 (69%)	18 (51%)	9 (60%)	0.59
ICS	10 (77%)	22 (63%)	11 (73%)	NA
Theophylline	0	1 (3%)	0	NA
Leukotriene modifier	0	1 (3%)	0	NA
OCS	3 (23%)	1 (3%)	1 (7%)	NA
Duration of follow-up (Months (Median [IQR]))	16 [10, 43]	12 [6, 26]	18 [5, 26]	0.63
IV spirometry Post BD (Median [IQR])				
FVC (Liter)	2.76 [2.00, 3.58]	2.90 [2.22, 3.71]	2.51 [1.97, 3.33]	0.56
FVC (% predicted)	79 [74, 94]	79 [65, 90]	80 [71, 84]	0.73
FEV1 (Liter)	1.26 [1.03, 1.95]	1.51 [0.88, 2.14]	1.33 [1.05, 1.68]	0.84
FEV1 (% predicted)	54 [40, 64]	55 [38, 74]	51 [45, 61]	0.91
FEV1/FVC	0.52 [0.42, 0.58]	0.5 [0.41, 0.60]	0.52 [0.45, 0.58]	0.94
6 MWD in meters (Median [IQR])	300 [246, 325]	268 [224, 354]	276 [215, 300]	0.58
mMRC (Median [IQR])	2 [1, 2]	2 [1, 3]	3 [3, 4]	0.002
BMI < 21 (%)	0 (0%)	5 (15%)	2 (14%)	NA

Notes: P value was generated by Kruskal–Wallis test. NA= Unable to perform Chi-square calculations since it did not meet criteria of expected values being greater than 1.0 and at least 20% of the expected values to be greater than 5.
Abbreviations: IQR, interquartile range; SABA, short-acting β-agonist; SAMA, short-acting muscarinic antagonist; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist; ICS, inhaled corticosteroid; OCS, oral corticosteroid; IV, initial visit; BD, bronchodilator; FV, follow-up visit; FVC, Forced Vital Capacity; % FVC, percent predicted FVC; FEV1, Forced Expiratory Volume in 1 s; %FEV1, percent predicted FEV1; 6MWD, six-minute walk distance; mMRC, modified Medical Research Council dyspnea scale; BMI, body mass index.

who continue to worsen in BODE scores have precipitous decline in %FEV$_1$, 6MWD, and mMRC score. Fourth, patients who experience significant improvement in BODE score quartiles have most of their improvements occurring in the subjective dyspnea and activity tolerance measured by mMRC and 6MWD rather than the airflow capacity measured by FEV$_1$.

There are several potentially clinically significant findings worth mentioning in our study. First, a retrospective chart review in US from 1999 to 2008 reported that only 55% patients diagnosed with COPD had completed spirometry.[3,24] Similarly, in Sweden, retrospective chart review between 2000 and 2003 showed that of the patients with a new diagnosis of COPD, only 59% were evaluated with spirometry; of patients who completed spirometry, only 30% met GOLD criteria for the diagnosis of

COPD.[4] Similar to these studies, our study confirms the longstanding problems with accurately establishing the diagnosis of COPD based on the "irreversible airflow limitation" as a primary criterion. Strength of our study is the accurately characterized COPD diagnosis, phenotypes and severity.

Second, characteristics of COPD patients in our study are quite comparable to other studies involving IMDM. Our literature review discovered 25 clinical trials in a Cochrane review of IMDM interventions for the patients with COPD. These studies include 2997 patients with mean age 68 years, mean FEV1% predicted 44% (range 28–66%) and ranges of follow up from 3 to 24 months.[12] While this review shows significant improvement in health-related quality of life, 6MWD, respiratory-related hospital admissions and all-cause hospital days per patient, other prospective trials

Table 4 Change Between Initial Visit and Follow-Up Visit Within Each BODE Quartile Group

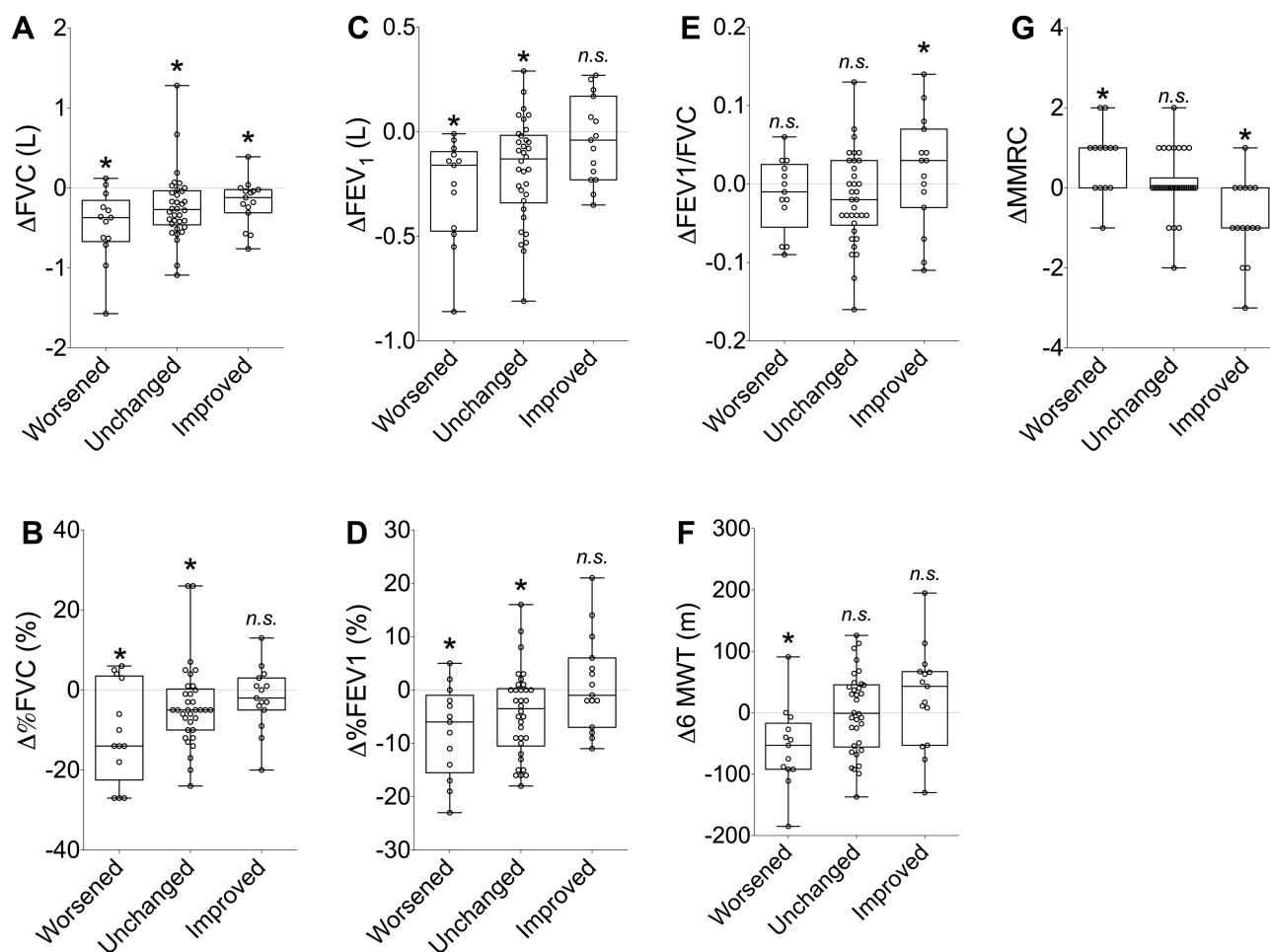| Change Between IV and FV	BODE Quartile Group	Median [95% CI]	P value
FVC Change (Liter)	Worsened	−0.37 [−0.71,-0.27]	0.002[a]
	Unchanged	−0.27 [−0.41,-0.09]	<0.001[a]
	Improved	−0.12 [−0.31,-0.02]	0.013[a]
FVC Change (% Predicted)	Worsened	−14 [−27, −4]	0.011[a]
	Unchanged	−5 [−7, −1]	0.003[a]
	Improved	−2 [−5, 3]	0.40[a]
FEV1 Change (Liter)	Worsened	−0.16[−0.49, −0.08]	<0.001[a]
	Unchanged	−0.13[−0.28,-0.05]	<0.001[a]
	Improved	−0.04[−0.23, 0.17]	0.2[a]
FEV1 Change (% Predicted)	Worsened	−6[−17, 0]	0.007[a]
	Unchanged	−3.5[−9, 0]	0.003[a]
	Improved	−1[−7, 6]	0.86[a]
FEV1/FVC Change	Worsened	−0.01[−0.08, 0.03]	0.44[a]
	Unchanged	−0.02[−0.04, 0.01]	0.062[a]
	Improved	0.03[−0.03, 0.7]	0.37[a]
6 MWD Change (Meters)	Worsened	−53[−92, −7]	0.012[a]
	Unchanged	−1[−25, 40]	0.92[b]
	Improved	43[−53, 67]	0.23[b]
mMRC Change	Worsened	1[0, 1]	0.031[a]
	Unchanged	0[0, 0]	0.48[b]
	Improved	−1[−1, 0]	0.016[c]

Notes: P value was generated by Wilcoxon Rank Sum test. Groups with the same superscript ([a], [b] or [c]) accompanying the 95% confidence interval for the median change from V1 to V2 indicate that the between group comparison for the median change was not statistically different at the p<0.05 significant level.
Abbreviations: CI, confidence interval; FVC, forced vital capacity; %FVC, percent predicted FVC; FEV1, forced expiratory volume in 1 s; %FEV1, percent predicted FEV1; 6MWD, six-min walk distance; mMRC, modified Medical Research Council dyspnea scale; BMI, body mass index.

with IMDM show no changes in primary outcomes (health-related QOL) and secondary outcomes (MMRC, smoking behaviors, and health care usage including COPD exacerbations and admissions).[12,13] Our study, while small in size, provides more insights into the reasons for these conflicting reports. It is likely that patients with COPD may have individually defined paths to their clinical courses regardless of the IMDM. However, IMDM optimizes the chances of those patients with COPD who have potentials to improve.

Third, since imputed variables for BODE scores are modifiable, BODE score can be used as a tool to evaluate the effectiveness of therapeutic interventions.[21] Effectiveness of bronchodilator and anti-inflammatory therapies can be construed from improvement in FEV_1 between pre- and post-IMDM. Therapeutic effectiveness in this aspect will reflect establishing a correct diagnosis, optimally selecting bronchodilator and/or anti-inflammatory inhalers, and consistent and effective teaching for inhaler techniques. It is possible that bronchodilator responsiveness

may predict the potential magnitude of therapeutic effects in FEV_1 but our data do not suggest that. Numerous studies have reported poor inhaler technique is present in up to two-thirds of patients with COPD.[25–29] Experience in our COPD clinic past 10 years indicates that the prevalence of poor inhaler technique is well above 90% regardless of socio-economic and/or educational background. Repeated and dedicated education is required to make clinically significant differences. The improved group experienced the smallest decrease in FVC between V1 and V2 without statistical significance. This relation indirectly suggests that these patients may be able to better maintain their respiratory mechanics and strength. However, our study was not designed to probe these questions. Changes in 6MWD are an important predictive parameter, but may only be possible when comprehensive optimization of the clinical management is achieved with IMDM.[20] Changes in mMRC are a bit difficult to explain, but it seems to correlate with improvement in 6MWD distance and stable FEV_1. There may be positive psychologic impact as these patients

Figure 2 Change between V1 and V2 within each BODE quartile group (**A-G**). Groups with the same superscript (* and n.s.) accompanying the 95% confidence interval for the median change from V1 to V2 indicate that the between group comparison for the median change was not statistically different at the p<0.05 significant level. *p<0.05.
Abbreviation: n.s., not significant.

receive personal counseling of their disease management with concrete descriptions of "possible items to improve"; FEV_1 with better choice of medications, technique, and adherence; 6MWD with completion of pulmonary rehabilitation; adherence to medical therapy; and smoking cessation. Instead of continually hearing the "terminal nature" of COPD prior to coming to our clinic, presentation of concrete road-map to "get better" during our IMDM may have provided positive impact on their psychologic state.

Fourth, our study has substantially benefited from standardizing outcomes and organizational structure under the Joint Commission certified COPD program. This has forced our clinic to establish clinically relevance metrics to monitor in outpatient clinic settings. As a part of this effort, EMR-based monitoring of BODE scores has been established in addition to mandatory consideration for a standard diagnostic algorithm and pulmonary rehabilitation during the initial visit, coordinated counseling and education for

inhalers, disease management and cigarette smoke cessation, and other IMDM packages. The IMDM was clearly defined and distributed to all COPD clinic team members, so that the IMDM program has been consistently administered over past 12 years. Therefore, IMDM in our study has been highly organized and standardized with experienced personnel as a part of routine clinical care, which is different than some of the larger-scale studies in the past.

Fifth, one of the most important components of our IMDM is the commitment to patient education and persistent follow-up. Three important areas of the educational interventions are inhaler use techniques, self-disease management to monitor disease status at home, and smoking cessation. Inhalers use techniques have been poorly taught in an outpatient care setting, and routinely more than 50% of IMDM education time was used repeatedly during initial and follow-up visits for this deficit. Ability to self-manage COPD can also be quite challenging due to numerous

factors. Creation of simple color-coded assessment tool ([Supplemental Figure 2](#)) and repeated education were necessary to empower patients to manage their COPD better. Rate of smoking cessation is confounded due to the fact that our patients are highly motivated to quit due to their severity. However, 33% quit rate seems still impressive and again likely due to repeated multidisciplinary interventions managed by COPD clinic navigators.

There are also several limitations of our study which merit discussion. First, the size of the study is small. Therefore, careful interpretation and conclusion of our primary findings are warrantied; discovery of three COPD phenotypes based on their responsiveness to IMDM. Second, IMDM interventions are individualized based on patients' unique needs. While all components of the IMDM are consistently administered to each patient, durations, and intensity for each IMDM component are not strictly set due to our understanding that individualized needs for each patient may be different. This flexibility in how the IMDM is administered is a potential weakness of our study as a source of confounding factors. However, this kind of flexible IMDM is also what we probably need to make real impact on the care for patients with COPD. Third, we have a number of patients who did not complete follow-up evaluation. While this is a potentially confounding factor, subjects with and without follow-up are comparable at the time of their initial visits. Fourth, our study is a single-arm, historical observational study with an intervention. Having a placebo arm would have enhanced the quality of our data, but we also believe that clear separation of our patients based on their trajectory of the BODE quartile demonstrates potentially clinically significant impact on the outcomes of COPD patients with IMDM. This is also a study conducted in a single tertiary academic center. Therefore, generalizability may need to be carefully weighted. Our program has received significant institutional support in personnel and organization under the Joint Commission certification processes over past 12 years. While this is a desirable circumstance, similar resources may not be available or can be duplicated in a smaller clinical setting. Finally, while we use BODE scores and quartiles to suggest potential survival impact of our IMDM, obviously this is less desirable than actual mortality.

Conclusion

Our study demonstrates that an IMDM program with well-trained, -organized, -funded and flexible components could be potentially highly effective in altering clinical outcomes of a subset of patients with COPD. These changes can have clinically meaningful impact based on changes in BODE scores. These improvements, however, seems improbable in other subsets of patients regardless of how intense the clinical intervention is. Future studies are necessary to determine the factors that can differentiate these subgroups because such information can be useful in managing patients with COPD.

Abbreviations

COPD, chronic obstructive pulmonary disease; GOLD, global obstructive lung disease initiative; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; 6MWD, six-minute walk distance; mMRC, modified medical research council; CAT, COPD assessment test; IMDM, integrated multidisciplinary disease management; IQR, interquartile range; %FEV1, percent predicted FEV1; %FVC, percent-predicted FVC; BMI, body mass index.

Acknowledgments

Disclosure

The authors report no conflicts of interest in this work.

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