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Implications of frailty in COPD exacerbations

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Introduction

The extrapulmonary manifestations of chronic obstructive pulmonary disease (COPD) patients are similar to symptoms of frailty, a geriatric syndrome. This study was designed to identify the relation between frailty and patient outcomes during a COPD exacerbation.

Methods

This retrospective study identified 10,235 patients hospitalized for COPD exacerbation, as well as 16 laboratory tests included in a frailty index that have been linked to frailty. Patients were divided into less frail (0-8 positive laboratory values) and more frail (9-16 positive laboratory values) groups. The primary composite endpoints were mechanical ventilation, ICU length of stay, readmission, and discharge status.

Results

Of the 10,235 patients in this study, 205 (2%) classified as more frail. These patients were 6.3 times more likely to need MV (SDD 0.000). If they were admitted to the ICU, they spent 29 hours longer (SDD 0.002) than the less frail group. The more frail group was discharged to hospice or expired (35.2% vs. 3.5%), home (40.6% vs. 74.4%), acute/subacute rehabilitation (16.8% vs. 13.8%), compared to the less frail group. There was no statistical difference between high risk of frailty and less frail in terms of hospital readmissions (SD 0.604) or having pulmonary service consulted during the hospital admission (SDD 0.398).

Conclusion

We found that highly frail patients have poorer outcomes than their less frail counterparts including longer ICU length of stay and less possibility of discharge home from the hospital. Interestingly, there was no statistical significance in terms of hospital readmissions.

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Introduction and background

Chronic obstructive pulmonary disease (COPD) is a public health concern that has a high financial burden on the US healthcare system. Of the approximately $50 billion in annual direct costs for COPD, acute exacerbations account for $13.2 billion in spending. Hospital readmissions and longer length of stay lead to higher patient morbidity and mortality, which can be seen as more markedly in patients with additional comorbidities, such as frailty. Frailty is a clinical state of physical, psychological, and social vulnerability that requires increased care. In other words, it is a syndrome in which a person has reduced physiologic reserve to return to homeostasis. There is a higher prevalence of frailty in patients with COPD aged 55 years or older, compared with the general population (Shah). Patients who are severely frail experience more readmissions than non-frail patients. Image 1 highlights the importance of frailty in pulmonary and critical care medicine in terms of performance status and susceptibility to exacerbations of chronic lung diseases, as well as morbidity and mortality risk.

Frailty is associated with decreased mobility, decreased cognitive function, increased risk for falls, and malnutrition, which can also be seen with chronic conditions such as COPD (Uchmanowicz). The exact reason for this association is unknown, but both conditions share certain pathophysiological mechanisms such as chronic inflammation, immune system dysfunction, and impaired neuroendocrine regulation. Frail patients also tend to accumulate higher healthcare costs due to more visits to the emergency room and more hospital admissions. Factors linked to frailty include older age greater than 85 years old, female gender, African American race, and lower income/educational levels (Park).

A systematic review and meta-analysis published in Chest in 2018 selected 27 studies regarding the association between COPD and frailty. Most of the studies identified COPD based on the GOLD criteria, while three were based on the American Thoracic Society guidelines. They took into account some community-dwelling patients and other studies using hospitalized patients. Frailty was evaluated using the Fried criteria (Table 1), among other frailty indices. The authors found that older patients with COPD have a two-fold increased odds of frailty and identified the need to investigate any potential negative effects associated with the coexistence of these conditions.

Assessing for frailty has been done using different methods, usually including a phenotypic definition (based on the presence of three out of five deficits, including walking speed, hand grip strength, activity levels, weight loss, and exhaustion), and a subjective multidimensional approach that includes psychosocial and physical responses from the patient. A cross-sectional analysis (Gale) that studied community-dwelling patients with and without COPD using a comprehensive geriatric assessment (CGA) questionnaire and frailty index (FI-CGA) was performed to find an association between frailty and COPD. They concluded that patients with COPD were more frail than a similar population (in terms of age, gender, and BMI) that was free of respiratory disease.

Park, et al performed a similar study aiming to describe frailty, identify which demographic and clinical characteristics lead to frailty, and examine the relationship between frailty and health-related outcomes of COPD. This study was a secondary cross-sectional study using data from the National Health and Nutrition Evaluation Survey. Frailty was defined using nine criteria (nutrition, mobility, physical activity, strength, sensory functions, cognition, social relations, social support) and demographic information, including healthcare utilization, was based on self-reported questions. They concluded that frailty is

important in the COPD population, however, it recommended further studies to understand the relation of the two using objective measures for the definition of frailty.

Per Bernabeu-Mora, et al., severely frail patients were much more likely to be readmitted to the hospital than non-frail patients and recommended that identifying patients with frailty for targeted interventions may reduce early readmission rates.

Another study published in the Journal of Gerontology was performed in the Netherlands in which the researchers aimed to identify the prevalence and associated mortality risk in older patients with COPD. They found that the prevalence of frailty was higher in patients with COPD than those without COPD and that frail patients had worse survival outcomes. They organized COPD patients based on spirometry readings and Global Initiative or Chronic Obstructive Lung Disease (GOLD) classification, and measures frailty based on the phenotypic definition by Fried as detailed in Table 1.

Frailty has typically been defined on the basis of phenotype, but newer studies have aimed at defining it on the basis of laboratory findings alone or in conjunction with phenotypic assessments. Howlett et al used data from the Canadian Study of Health and Aging (CSHA) in 2014 to develop a frailty index using 21 routine laboratory values (FI-Lab) (Table 2) along with blood pressure and pulse. This was a cohort study of health issues in patients 65 years or older. The FI-Lab was only calculated if at least 70% of the values were available for a given patient. The authors concluded that the FI-Lab identified older adults at an increased risk of death and recommended further study into the use of this tool. The same group later (Blodgett et al) used the FI-Lab and applied it to community-dwelling males from the longitudinal European Male Ageing Study (EMAS) in order to predict the risk of adverse health outcomes. They concluded that FI-Lab detected an increased risk of health outcomes alone and in combination with a clinical frailty index based on self-reported performance-based and clinical deficits (FI-Clin), but recommended further study for the feasibility of using the FI-Lab as a frailty screening tool in hospital settings.

The former studies from Howlett and Blodgett set the groundwork for another study by Ritt et al from the Institute for Biomedicine of Ageing in Germany in which they studied 307 hospitalized patients aged 65 years or older in the geriatric ward. The study used the FI-Lab, however, it did not take into account blood pressure or pulse as was done in the previous studies. They solely used blood and urine laboratory results taken at the end of the patient's hospitalization (before discharge) and calculated it if at least 80% of the laboratory variables were available for any given patient. The authors concluded that FI-Lab could be a valuable tool to use for the estimation of mortality risk on hospitalized patients on geriatric wards.

We believe that there is an important correlation between COPD and frailty that can be studied by measuring frailty using the FI-Lab alone, which includes routine laboratory tests commonly ordered in the emergency room and throughout a patient's hospitalization. Thus far, it is not standard practice to consult a geriatrician in the acute setting of a COPD exacerbation, so we wanted to identify if there is any significance in evaluating for frailty and what it could mean in terms of risk stratifying for hospital readmission, morbidity, mortality, outcomes, and ICU requirement.

Methods

This is a retrospective study in which we identified patients who were admitted to different facilities within the Healthcare Corporation of America (HCA) Eastern Florida Division from July 1st, 2017 to

December 31st, 2017. We selected 10,235 patients from our electronic medical record (EMR) database who were hospitalized for COPD exacerbation. Inclusion criteria were adults 18 years or older, mean age of 71.15 (SD + 12.885) (Table 4), with an ICD-10 coded diagnosis of COPD (ICD-10 J44.9 Chronic obstructive pulmonary disease, unspecified; ICD-10 J44.1 Chronic obstructive pulmonary disease with (acute) exacerbation; ICD-10 J44.0 Chronic obstructive pulmonary disease with acute lower respiratory infection). We also selected 16 laboratory tests included in the FI-Lab index that have been linked to frailty. Patients were divided into two groups: less frail (0 to 8 positive laboratory values) and more frail (9 to 16 positive laboratory values). We reviewed the relation of the two groups to the primary composite end points: mechanical ventilation, ICU length of stay, readmission, and discharge status (expired, hospice, rehabilitation facility, or home). A statistician was recruited to help with the data analysis. The logistic and linear regressions were ran using the following variables: frailty indicator, age, sex indicator. The ANOVA test was run on the frailty indicator. Odds ratio was used to correlate the composite primary endpoints listed above, except for the discharge status where we used a Chi-square test of homogeneity on the three groups of discharges: home (HO), health rehab (HR), hospice expired (HE), and other discharge based on frailty indicator with a corresponding post-hoc z-test of two proportions.

Results

The total number of patients in our study admitted for COPD exacerbation (N = 10,235) included 9,991 that were classified as low risk of frailty and 244 that were classified as high risk of frailty. In the low risk subgroup, 4,646 were males and 5,345 were females, with a mean age of 71 years. In the high risk subgroup, 139 were males and 105 were females, with a mean age of 74 years.

Variables for a logistic regression on ventilator indicator found to be a 0.05 significance level were frailty indicator ($p<0.001$) and sex indicator ($p=0.001$). This results in an adjusted odds ratio of 6.29 with a 95% confidence interval of (4.54, 8.72) for the frailty indicator and an adjusted odds ratio of 1.40 with a 95% confidence interval of (1.15, 1.70) for sex indicator. In other words, patients who were considered more frail had 6.29 times higher odds of requiring mechanical ventilation, and of these, males had 1.40 times higher odds.

Variables for logistic regression on ICU indicator found to be significant at a 0.05 significance level were frailty indicator ($p<0.001$) and sex indicator ($p<0.001$). We saw an adjusted odds ratio of 4.12 with a 95% confidence interval of (3.18, 5.35) for the frailty indicator and an adjusted odds ratio of 1.33 with a 95% confidence interval of (1.19, 1.48) for the sex indicator. The variable for a linear regression on ICU length of stay (in hours) at a 0.05 significance level was frailty indicator ($p=0.002$). This regression only included patients that had an ICU stay (N=1593), resulting in a coefficient of 28.97 hours with a 95% confidence interval of (10.36, 47.58) for the frailty indicator. This basically means that patients who were more frail had a 28.97 hour longer ICU stay than patients who were less frail.

Variables for a logistic regression on readmission indicator at a 0.05 significance level were age ($p<0.001$), which resulted in an adjusted odds ratio of 0.993 with a 95% confidence interval of (0.989,0.997) for age. This leads to an adjusted odds ratio of 1.007 times increase in the odds that there is no readmission.

Discharge

Regarding the discharge status, discharge to hospice or expired was 35.2% vs 3.5%; discharge to home was 40.6% vs 74.4%; discharge to acute/subacute rehabilitation was 16.8% vs 13.8% in the more frail group versus less frail group,

A Chi-square test of homogeneity was ran on the three groups of discharges to home (HO), health rehabilitation (HR), hospice/expired (HE), and other discharge based on frailty indicator with a corresponding post-hoc z-test of two proportions. The Pearson Chi-square test of homogeneity gave $\chi 2(3) = 597.31$, $p < 0.0005$, indicating that the proportions were significantly different across more frail versus less frail patients. The cross tabulation shows the post-hoc z-tests of two proportions with a Bonferroni correction. There were statistically significant differences ($p<0.05$) in the proportion of patients with discharge status Hospice/Expired (more frail: N=86, 35.2%; less frail: N=353, 3.5%) and discharging to home (more frail: N=99, 40.6%; less frail: N=7436, 74.4%) for more frail and less frail patients. This implies that more frail patients were significantly more likely to be discharged to hospice o expired than less frail patients, and that less frail patients were significantly more likely to be discharged to home than more frail patients.

Discussion

This study was performed to investigate the implications of frailty in patients with COPD. ICU admission and discharge disposition has been linked to healthcare cost, as patients who require ICU admission, end up dying in the hospital, or are discharged to a long term facility end up utilizing more healthcare resources and subsequently increasing costs. Patients who are more frail tend to be discharged more commonly to long term facilities, adding to healthcare utilization. Early identification of frailty in these patients may lead to overall reduction of healthcare costs by tailoring hospital care to their functional status, including early discussions of advance directives in the outpatient setting (Mulpuru).

We found that more frail patients required longer ICU length of stay and longer time on mechanical ventilation. Interestingly, there was no statistical significance in hospital readmission rates in more frail patients as compared to their less frail counterparts.

There were several limitations of our study. Firstly, this was a retrospective study in which data set was obtained via a statistician using our electronic medical records, so we were unable to obtain information regarding COPD severity and comorbidities. There was indeed a correlation between COPD and frailty, however the results were not adjusted for comorbidities. Secondly, our sample was obtained using ICD 9 and ICD 10 coding for COPD exacerbation, so we did not have a spirometric diagnosis for the patients to organize them according to GOLD criteria. Another limitation stems from the fact that the frailty index used was mainly tested on community-dwelling men, which is different from the population included in our study, which may lead to challenges in applicability to the general population.

Future studies should be performed in a prospective manner, identifying patients who have spirometry data so that they may be classified according to GOLD criteria. It would also be interesting to use other scores regarding comorbidities, such as the Charlson score; as well as the LACE index that predicts 30-day hospital readmission, although this score has been mainly validated for use in congestive heart failure patients.

Conclusion

It is important to identify the implications of frailty in COPD exacerbations because it can help risk stratify patients who may or may not be candidates for invasive procedures or who may be able to fully reap the benefits of pulmonary rehabilitation. Further studies should aim at standardizing a frailty index

that can be applied to a more general population, and to quantify healthcare utilization of the more frail patients who have COPD.

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Appendix

Table 1. Frailty as defined by Fried et al

Component of frailty	
Shrinking	Unintentional weight loss of ≥10 pounds in prior year or ≥5% of body weight in prior year
Weakness	Hand grip strength in the lowest 20% at baseline (adjusted for gender and body mass index)
Poor endurance and energy	Self-report of exhaustion associated with stage of exercise reached in graded exercise testing (predictive of cardiovascular disease)
Slowness	The slowest 20% of the population based on time to walk 15 feet
Low physical activity level	The lowest quintile of physical activity was identified for each gender based on a weighted score of kilocalories expended per week.
	3 or more = Frail 1-2 = Pre-frail 0 = Robust

Table 2. Clinical and laboratory data used to construct FI-Lab

Variables	
Albumin AST BP, supine systolic BP, supine diastolic Calcium Creatinine Folate Folate RBC Glucose, fasting	Phosphorus, inorganic Potassium Protein, total Sodium TSH Thyroxine T4, free Urea VDRL

Hemoglobin Mean corpuscular volume Phosphatase, alkaline	Vitamin B12 White blood cells

Table 3. Labs used for determination of Frailty

Proc_Mnem	name	low_normal	high_normal	Units
ALB	Albumin (Serum)	3.2	5	g/dL
ALT	SGPT (ALT)	10	60	Units/L
AST	SGOT/AST	10	40	Units/L
BILT	TOTAL BILIRUBIN	0.1	1.2	mg/dL
BUN	Urea Nitrogen Blood (BUN)	3	22	mg/dL
CA	Calcium (Serum)	7.7	10.2	mg/dL
CREAT	Creatinine (Serum)	0.43	1.3	mg/dL
HCT	Hematocrit	34.7	52	%
HGB	Hemoglobin	11.8	18	g/dL
K	Potassium (Serum)	3.5	5.2	mmol/L
MCV	MEAN corpuscular VOLUME	81	97	fl
NA	Sodium (Serum)	135	145	mmol/L
PLT	Platelet Count	147	400	10^3/uL
RBC	RED CELL COUNT	3.8	5.9	10^6/uL
TP	Total Protein (Serum)	5.5	8.7	g/dL
WBC	WHITE BLOOD COUNT	3.5	20	10^3/uL

Frailty was based on the labs in the following table. Abnormal values were totaled for lab values which did not fall between the low_normal and high_normal values. Patients were considered frail if they fell into abnormal values for 9 or more of the 16 chosen labs.

Table 4. Patient demographics

Descriptive Statistics

	N	Minimum	Maximum	Sum	Mean	Std. Deviation
Frailty indicator	10235	0	1	244	.02	.153
Age	10235	20	90	728249	71.15	12.885
Sex indicator	10235	0	1	4785	.47	.499

nsurance indicator	10235	0	1	9714	.95	.220
Ventilator indicator	10235	0	1	441	.04	.203
CU indicator	10235	0	1	1593	.16	.363
CU hours	1593	.166666667	800.8333333	155422.2667	97.5657669	93.92979374
Readmission indicator	10235	0	1	2471	.24	.428
Pulmonary indicator	2379	0	1	174	.07	.260
DC Home indicator	10235	0	1	7535	.74	.441
DC Rehab indicator	10235	0	1	1420	.14	.346
Hospice/expired indic	10235	0	1	439	.04	.203
Valid N (listwise)	573					

DC = Discharge

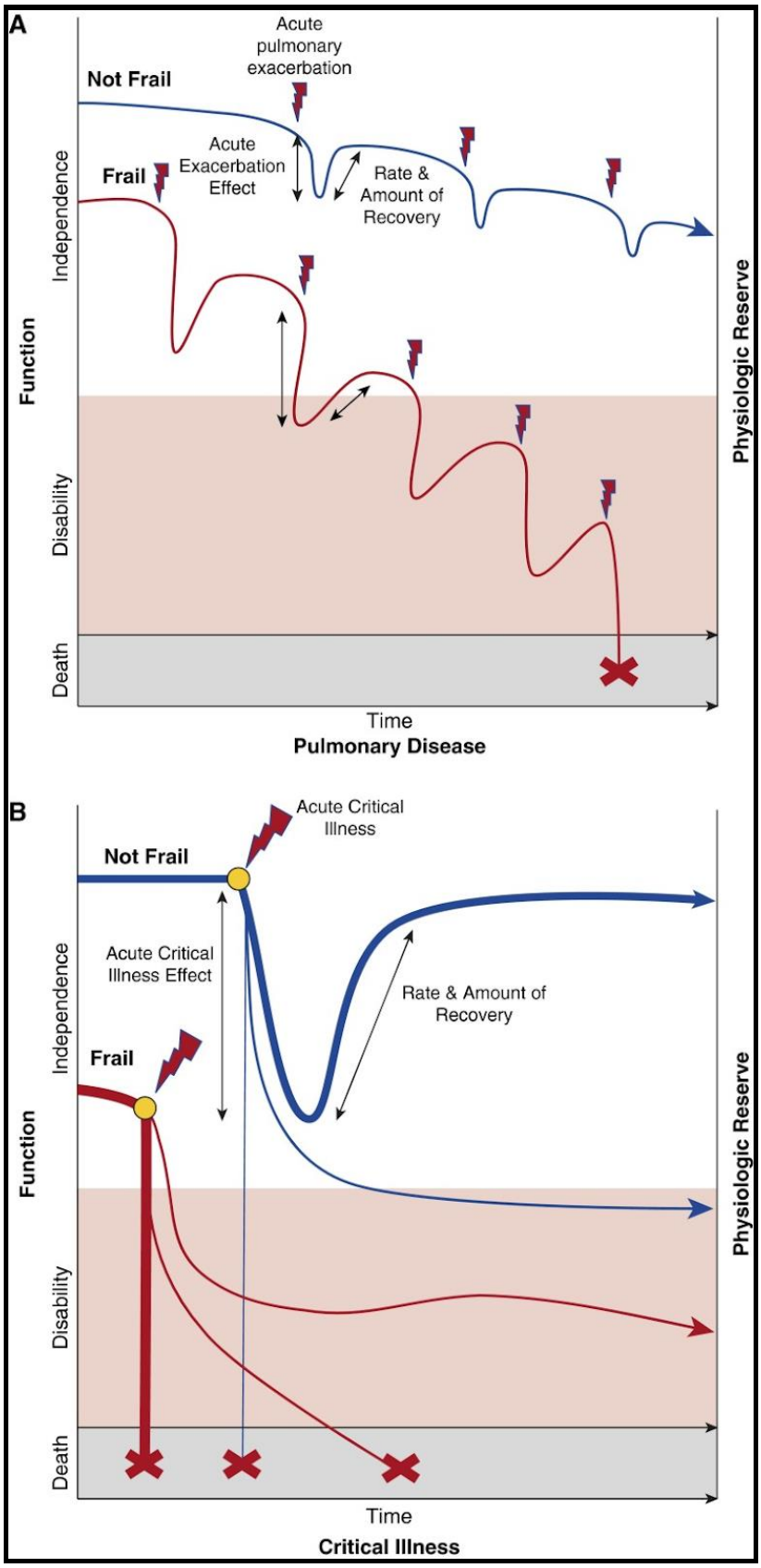
A
Acute pulmonary exacerbation
Not Frail
Frail
Acute Exacerbation Effect
Rate & Amount of Recovery
Function
Independence
Disability
Death
Physiologic Reserve
Time
Pulmonary Disease
B
Acute Critical Illness
Not Frail
Acute Critical Illness Effect
Rate & Amount of Recovery
Frail
Function
Independence
Disability
Death
Physiologic Reserve
Time
Critical Illness

Image 1. (A) Hypothetical trajectories of functional status for patients experiencing recurrent acute exacerbations of chronic lung disease who are frail (red line) and not frail (blue line). Frail patients are susceptible to more frequent exacerbations with less recovery in between, resulting in faster loss of functional status, earlier onset of disability, and a shorter lifespan. (B) Hypothetical trajectories for patients who are frail (red line) or not frail (blue line) prior to becoming critically ill. The thickness of the trajectory lines represents the proportion of patients in each trajectory. For a given insult, frail patients are susceptible to becoming critically ill sooner. Patients who are frail prior to critical illness are more likely to die in the hospital and more likely to develop chronic critical illness or severe disability leading to an early death. If they survive their critical illness, they are prone to recover functional status more slowly or develop permanent disability and a shorter lifespan than those who are not frail.

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