Original research

Frailty subtypes and recovery in older survivors of acute respiratory failure: a pilot study

Matthew R Baldwin [ID],[1] Lauren R Pollack,[2] Richard A Friedman,[3] Simone P Norris,[1] Azka Javaid,[1] Max R O'Donnell,[1] Matthew J Cummings,[1] Dale M Needham [ID],[4,5] Elizabeth Colantuoni,[4,6] Mathew S Maurer,[7] David J Lederer [ID][1,8]

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ABSTRACT

Background Identifying subtypes of acute respiratory failure survivors may facilitate patient selection for post-intensive care unit (ICU) follow-up clinics and trials.

Methods We conducted a single-centre prospective cohort study of 185 acute respiratory failure survivors, aged ≥65 years. We applied latent class modelling to identify frailty subtypes using frailty phenotype and cognitive impairment measurements made during the week before hospital discharge. We used Fine-Gray competing risks survival regression to test associations between frailty subtypes and recovery, defined as returning to a basic Activities of Daily Living disability count less than or equal to the pre-hospitalisation count within 6 months. We characterised subtypes by pre-ICU frailty (Clinical Frailty Scale score ≥5), the post-ICU frailty phenotype, and serum inflammatory cytokines, hormones and exosome proteomics during the week before hospital discharge.

Results We identified five frailty subtypes. The recovery rate decreased 49% across each subtype independent of age, sex, pre-existing disability, comorbidity and Acute Physiology and Chronic Health Evaluation II score (recovery rate ratio: 0.51, 95% CI 0.41 to 0.63). Post-ICU frailty phenotype prevalence increased across subtypes, but pre-ICU frailty prevalence did not. In the subtype with the slowest recovery, all had cognitive impairment. The three subtypes with the slowest recovery had higher interleukin-6 levels (p=0.03) and a higher prevalence of ≥2 deficiencies in insulin growth factor-1, dehydroepiandrosterone-sulfate, or free-testosterone (p=0.02). Exosome proteomics revealed impaired innate immunity in subtypes with slower recovery.

Conclusions Frailty subtypes varied by prehospitalisation frailty and cognitive impairment at hospital discharge. Subtypes with the slowest recovery were similarly characterised by greater systemic inflammation and more anabolic hormone deficiencies at hospital discharge.

Key messages

What is the key question?
► Can we identify clinically and biologically distinct frailty subtypes in older survivors of acute respiratory failure?

What is the bottom line?
► We identified five frailty subtypes using frailty phenotype and cognitive impairment clinical measurements made during the week before hospital discharge.

Why read on?
► Acute respiratory failure survivors are grouped into meaningfully different frailty subtypes that might help in selecting patients for post-intensive care unit follow-up clinics and clinical trials investigating novel interventions to improve survivors' recovery. Persistent systemic inflammation and multiple anabolic hormone deficiencies at hospital discharge similarly characterise several frailty subtypes with slower recovery, and may represent therapeutic targets.

dysregulation that underlies post-ARF physical disability remains poorly understood.

Frailty is a syndrome wherein decreased reserves and dysregulation across multiple physiological systems result in functional limitations and vulnerability to new stressors.[14] Over the past decade, a majority of studies in frailty and critical care have shown that prehospitalisation frailty, measured by the clinician-assigned Clinical Frailty Scale score,[15] is independently associated with in-hospital mortality, long-term morbidity and mortality, and worse quality of life.[16] Assessing prehospitalisation frailty may help influence family discussions and clinical decision-making in the ICU. Less is known about post-ICU frailty and how it may influence mortality and physical recovery after the ICU. Discovering whether post-ICU frailty subtypes exist in ARF survivors, and investigating the potential underlying frailty mechanisms that may inhibit recovery has the potential to influence clinical care and research in ICU survivors. Specifically, identifying post-ICU frailty subtypes may inform how ARF survivors should be triaged for postacute palliative or rehabilitation care, and may help enrich

INTRODUCTION

Survivors of acute respiratory failure (ARF) often have substantial disability that is acquired or worsened during the intensive care unit (ICU) stay.[1–3] Consequently, about 30% of adult ARF survivors are discharged to a postacute care facility.[1 4] Even those discharged to home have lasting physical impairment.[5–8] Studies have begun to elucidate the mechanistic underpinnings of ICU-acquired muscle atrophy and myopathy,[9–13] but the multisystem

future post-ICU clinical trials that are aimed at improving ICU outcomes with patients most likely to have persistent post-ICU debilitation and response to rehabilitative and/or novel pharmacological interventions.

The Fried frailty phenotype (FP) domain measures of wasting, low activity, exhaustion, weakness and slowness, as well as measures of cognitive impairment capture many of the heterogeneous deficits observed in debilitated ARF survivors. We previously demonstrated the feasibility and validity of conducting a modified FP assessment in ICU survivors after the ICU, on the hospital ward, during the week before hospital discharge.[2 17] We showed that the FP, traditionally defined as deficits in ≥3 of 5 frailty domains, was independently associated with a nearly sixfold increased risk of mortality over 6 months.[17] However, we found that using the traditional cutoffs for continuous FP domain measures that were based on the lowest sex-specific quintiles of community-dwelling older adults in the Cardiovascular Health Study (CHS) were too sensitive for older ARF survivors. Seventy-three per cent of our study population was identified as phenotypically frail at hospital discharge, but we observed substantial heterogeneity in the rates of recovery in the following 6 months.

Latent class modelling was used to identify hyperinflammatory and hypoinflammatory ARDS subtypes with differential responses to higher positive end-expiratory pressure with mechanical ventilation and intravenous fluid resuscitation,[18 19] but latent class modelling has never been conducted in ARF survivors. Applying latent class modelling to FP domain measures in ARF survivors is appealing because it offers an agnostic assessment of how frailty domains may cluster in this study population.[20] Specifically, it allows measures of gait-speed, grip-strength and physical activity to be considered as continuous variables rather than categorical variables based on community-dwelling older adult population-specific lowest quintile cutoffs, and it removes the inherent measurement bias of assuming that each frailty domain measure is equally important. Given the heterogeneity of physical and cognitive deficits observed in older ARF survivors,[8] we hypothesised that a latent class analysis using FP and cognitive impairment measurements would reveal >2 clinically and biologically distinct frailty subtypes with different rates of functional recovery.

METHODS
Study design and participants
We examined ARF survivors enrolled in the Frailty and Outcomes in Critical Illness Survivors (FOCIS) study. Participants were ≥65 years old, received >24 hours invasive mechanical ventilation, non-invasive of positive pressure ventilation, or high-flow nasal cannula, and survived to hospital discharge. We enrolled only older adults (≥65 years old) because they make up the majority of adults with ARF,[4 21] because most ARF survivor cohort studies consist of predominantly middle-aged adults,[22 23] and because there remains a knowledge gap about how best to risk-stratify and identify older ICU survivors for targeted palliative, rehabilitative or therapeutic interventions. Participants were recruited from Columbia University Medical Center and the Allen Hospital, a Columbia University Medical Center-affiliated community hospital. See online supplemental E-Methods for exclusion criteria. Recruitment took place in two phases: a pilot cohort (n=22) was enrolled between February and August 2012 to ensure the feasibility of enrolling a larger cohort (n=163),[2] which was enrolled between May 2014 and June 2017. Since pilot and main cohort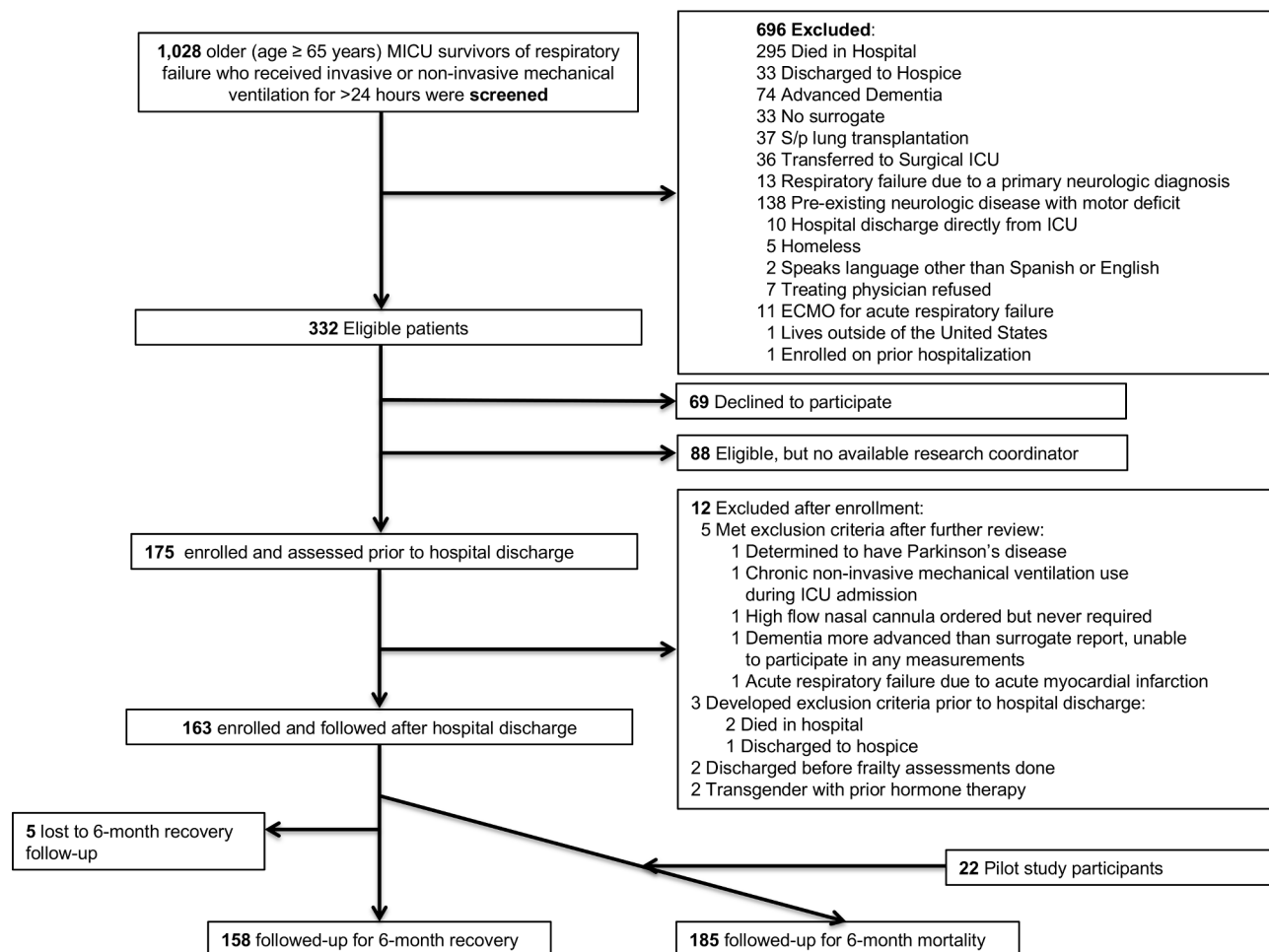 participants had identical inclusion/ exclusion criteria and baseline study measurements, all were included in the latent class analysis. We enrolled participants and their surrogates, and obtained informed consent for both.

Clinical measurements
The baseline assessment occurred during the week before hospital discharge after participants were transferred from the ICU to the medical ward. We measured the five Fried FP domains as we have previously reported and validated.[2 17] Briefly, we measured grip-strength, gait-speed and exhaustion, and asked about weight loss in the year prior to hospitalisation using CHS methodology.[24] We assessed the physical activity domain on the basis of report of activities performed 1 month prior to hospitalisation using the Duke Activity Status Index (DASI).[25] We previously demonstrated that substitution of the DASI for the Minnesota Leisure Time Physical Activity Questionnaire,[26] the original CHS measure of physical activity, improves the construct and predictive validity of the frailty phenotype assessment in ARF survivors.[17] We used previously validated DASI score cutoffs for low activity in older ARF survivors (men ≤ 12.5; women ≤10).[17] See online supplemental E-Methods and E-Table 1 for further details. Consistent with the CHS methodology,[24] we considered participants evaluable for frailty if they had at least three measurements of the five domains, and defined the post-ICU FP as being frail in ≥3 of the five domains. We assessed for cognitive impairment at the start of the baseline assessment on the general ward. We defined cognitive impairment as either delirium (evaluated using the Confusion Assessment Method-ICU), or in those without delirium, a score ≤2 on the Mini-cog test.[27 28] We used participant/surrogate interviews and medical records to assign a Clinical Frailty Scale score based on function 1 month prior to hospitalisation, with a score ≥ 5 representing pre-ICU frailty.[15] We assessed disability as the number of basic Activities of Daily Living (ADL) disabilities 1 month prior to hospitalisation based on participant/surrogate interviews, at hospital discharge based on interviews with participants and their nurses, and at 1, 3 and 6 months during in-person or telephone interviews with participants/surrogates.[29] We ascertained the date of death from surrogates, or from national death indexes. Criteria for querying the surrogate and additional demographic and clinical variables are described in the online supplemental E-Methods.

Laboratory measurements
We obtained a blood sample on the same day as the frailty measurements. We assessed serum interleukin-6 (IL-6), tumour necrosis factor soluble receptor-1 (TNFR1), insulin growth factor-1 (IGF-1), dehydroepiandrosterone-sulfate (DHEAs), sex hormone binding globulin and albumin (see online supplemental table E2 for assay details). We measured total testosterone and 25-OH vitamin D using liquid chromatography-mass spectrometry (see online supplemental E-Methods). We calculated the free testosterone level using the Vermeulen formula.[30] We defined vitamin D deficiency as <20 ng/mL.[31] We used the lowest sex-specific study population quartile to define hormone deficiency risk groups; the conventional approach used in landmark ageing studies.[32 33] Prior to the latent class identification of frailty subtypes, 20 non-frail and 25 post-ICU FP frail participants had serum exosome isolation and enrichment, and quantitative and qualitative proteomic analyses (see online supplemental E-Methods for further details including rationale for this approach).[34]

1,028 older (age ≥ 65 years) MICU survivors of respiratory failure who received invasive or non-invasive mechanical ventilation for >24 hours were **screened**

696 Excluded:
295 Died in Hospital
33 Discharged to Hospice
74 Advanced Dementia
33 No surrogate
37 S/p lung transplantation
36 Transferred to Surgical ICU
13 Respiratory failure due to a primary neurologic diagnosis
138 Pre-existing neurologic disease with motor deficit
 10 Hospital discharge directly from ICU
 5 Homeless
 2 Speaks language other than Spanish or English
 7 Treating physician refused
 11 ECMO for acute respiratory failure
 1 Lives outside of the United States
 1 Enrolled on prior hospitalization

332 Eligible patients

69 Declined to participate

88 Eligible, but no available research coordinator

175 enrolled and assessed prior to hospital discharge

12 Excluded after enrollment:
 5 Met exclusion criteria after further review:
 1 Determined to have Parkinson's disease
 1 Chronic non-invasive mechanical ventilation use
  during ICU admission
 1 High flow nasal cannula ordered but never required
 1 Dementia more advanced than surrogate report, unable
  to participate in any measurements
 1 Acute respiratory failure due to acute myocardial infarction
3 Developed exclusion criteria prior to hospital discharge:
 2 Died in hospital
 1 Discharged to hospice
2 Discharged before frailty assessments done
2 Transgender with prior hormone therapy

163 enrolled and followed after hospital discharge

5 lost to 6-month recovery follow-up

22 Pilot study participants

158 followed-up for 6-month recovery

185 followed-up for 6-month mortality

Figure 1 Study flow diagram. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Latent class analysis

We conducted a latent class analysis using the five FP domain measures and the presence versus absence of cognitive impairment as latent class indicator variables. We included cognitive impairment because it is an effect modifier of the association between frailty and recovery (see online supplemental figure E1).[35] We calculated sex-specific z-scores for grip-strength, gait-speed and DASI scores. Using MPlus V.7.2 software, we fit a latent class model using the full-information maximum likelihood assumption under the missing at random assumption. We selected the optimum number of classes based on (1) the Bayesian Information Criteria (BIC); (2) Bayes Factor; (3) model entropy; (4) the size of the smallest class; and (5), the Vuong-Lo-Mendell-Rubin (VLMR) likelihood ratio test.[20] We assigned each subject to the latent class for which he/she had the maximum posterior probability.

Characterisation of frailty subtypes

We compared clinical and biomarker variables across frailty subtypes using analysis of variance, Kruskal-Wallis, χ^2, or Fisher exact tests. We assessed individual proteome-wide differential protein expression between frailty subtypes using Limma,[36] and set significance at $p < 0.05$ with false discovery rate (FDR) < 0.2 and an absolute $\log_2$ fold change of > 0.2. We identified protein functional classes from the Reactome database of human biological pathways that differed between frailty subtypes using the Correlation Adjusted Mean Rank gene set test (CAMERA) at

$p < 0.05$ with FDR < 0.2.[37 38] We conducted an unsupervised clustering analysis and created heat maps of differentially expressed proteins based on three groups that were found by Limma and CAMERA (subtype 1, 2 and 3–5). We identified those proteins differentially expressed by Limma which belong to the Reactome protein functional classes identified by CAMERA in order to identify which proteins may be operative in the differential protein functional classes (see online supplemental E-Methods for details).

We created Kaplan-Meier plots for survival and recovery. We defined recovery as returning to an ADL disability count $\leq$ the prehospitalisation count within 6-month follow-up. We measured time to recovery as the number of days from ICU discharge until the date of the follow-up assessment at which recovery was first achieved (ie, hospital discharge, 1-month, 3-month or 6-month follow-up). Decedents were censored at the time of death if they died prior to recovery. We excluded from recovery analyses FOCIS pilot cohort participants who never had disability follow-up, and FOCIS main cohort participants who were lost to follow-up for posthospitalisation disability assessments. We estimated the 6-month recovery rate ratio across each increasing frailty subtype using Fine-Gray competing-risks survival regression models with death as the competing risk. Models were adjusted for age, sex, pre-existing ADL disability, comorbidity, and Acute Physiology and Chronic Health Evaluation (APACHE)-II score. We confirmed the proportional hazards assumption of the Fine-Gray models using

the Schoenfeld residuals test. We conducted a sensitivity analysis to assess for time-aggregation bias due to interval follow-up after hospital discharge (see online supplemental E-Methods for details).[39]

We planned to enrol 165 participants in the main cohort, because the original goal of this study was to determine whether the post-ICU FP was independently associated with 6-month mortality.[17] At this sample size, we estimated that we would have >80% power to detect a 6-month mortality rate ratio of 1.6 per SD change in frailty score in adjusted analyses. Power cannot be directly derived for latent class models. If the sample size is too small, the number of latent class indicators too high, and the quality of the latent class indicators is too low, then latent class model non-convergence is possible,[40] which we did not observe.

RESULTS
Identification of frailty subtypes
There were 185 FOCIS participants consisting of 22 pilot and 163 main cohort participants. Frailty assessments occurred a median (IQR) 1 (0–4) days prior to hospital discharge. Five main cohort participants (3%) were lost to follow-up for disability (figure 1). Frailty domain and cognitive impairment latent class indicator variable measure missingness ranged from 0.5% to 6% (online supplemental table E3). We fit latent class models ranging from one to six classes using all 185 participants. The BIC decreased as the number of classes increased, and the Bayes Factors' were >150 for all models up to a 5-class model, providing 'very strong' evidence that the additional classes added information to the model.[41] Entropy was >0.80 in three-class to six-class models, indicating good separation of classes for these models. The smallest class size became low at 14 participants in the six-class model. Using the VLMR test, two-class, three-class and five-class models were significant improvements over models with one fewer class (table 1). We retained a final five-class model based on these results. The average latent class membership probabilities for the five-class model ranged from 0.88 to 0.95, indicating high probabilities of class assignment. We subsequently refer to latent classes as frailty subtypes.

Frailty subtype clinical characteristics
Mean (SD) ages of frailty subtypes ranged from 71 (9) years in subtype 1 to 78 (8) years in subtype 5 (table 2). Fifteen (8.1%) had chronic critical illness, defined as a tracheostomy and >10 days of mechanical ventilation.[42] Subtype 1 appeared to be clinically 'robust'. None had prehospitalisation frailty or ADL disability, they had the shortest median (IQR) ICU length of stay (2 (2–6) days, p=0.01), only 9.5% had post-ICU cognitive impairment (p=0.003), and none were post-ICU FP frail (figure 2).

Subtype 2 appeared to be 'recoverably frail'. None had prehospitalisation ADL disability, but 44% were prehospitalisation frail. They had a higher APACHE II score and longer ICU length of stay than subtype 1, 57% were post-ICU FP frail, and 20% were discharged to a skilled-care facility. Longitudinal analyses revealed a high 6-month survival and recovery to independence in ADLs (see the Frailty subtypes, survival, and recovery section).

Subtype 3 appeared to be 'acutely frail', with 26% and 89% being prehospitalisation frail and post-ICU FP frail, respectively. They had the highest APACHE II score and longest ICU length of stay among all frailty subtypes, and 63% were discharged to a skilled-care facility. Subtype 4 appeared 'chronically physically frail' with 65% being prehospitalisation frail and 93% being post-ICU FP frail, with none having cognitive impairment. Subtype 5 were 'end-stage frail' with >90% having prehospitalisation frailty, post-ICU FP frailty and cognitive impairment.

Frailty subtype biomarker characteristics
Compared with those who were robust or recoverably frail (subtypes 1 and 2), those who were acutely frail, chronically physically frail, or end-stage frail (subtypes 3–5) had higher levels of IL-6 and TNFR-1 and more vitamin D deficiency during the week prior to hospital discharge (p=0.029, p=0.039, and p=0.047, respectively; figure 3A–C). The number of anabolic hormone deficiencies in either IGF-1, DHEAs, or free testosterone increased across frailty subtypes (figure 3D). While 94% of robust patients (subtype 1) had zero or one anabolic hormone deficiencies, 45% of end-stage frail patients (subtype 5) had two or three anabolic hormone deficiencies. Patients who were deficient in all three anabolic hormones were all either acutely

Table 1 Latent class model fit statistics for one to six latent classes of frailty subtypes in older adult acute respiratory failure survivors

| Classes | BIC | Bayes factor | Entropy | VLMR p value | Number of individuals per latent class | | | | | |
					1	2	3	4	5	6
2	2082		0.79	<0.01	123	62				
3	2039	>2×10¹⁰	0.84	0.014	96	22	67			
4	2024	1808	0.84	0.355	71	38	54	22		
5	2011	665	0.85	0.013	46	33	36	48	22	
6	2005	20	0.87	0.455	45	34	28	48	14	15

| Classes | Average latent class membership probabilities | | | | | |
	1	2	3	4	5	6
2	0.94	0.94				
3	0.94	0.9	0.89			
4	0.93	0.89	0.9	0.95		
5	0.88	0.95	0.91	0.88	0.95	
6	0.88	0.95	0.91	0.9	0.93	0.91

Bayes Factor compares the BIC of a model with *k* classes to the BIC of a model with *k*−1 classes. Entropy is a measure of latent class separation. VLMR likelihood ratio tests whether *k* number of classes provides improved model fit with a model using *k*−1 classes.
BIC, Bayesian Information Criterion; VLMR, Vuong-Lo-Mendell-Rubin.

Table 2 Characteristics of older adult acute respiratory failure survivors by frailty subtypes

Characteristic	All	Subtype 1	Subtype 2	Subtype 3	Subtype 4	Subtype 5	P value
Number of participants	185	21	49	35	46	34	
Demographics							
Age in years, mean (SD)	74 (8.1)	71 (8.8)	73 (7.8)	72 (6.5)	76 (8.7)	78 (7.6)	<0.001
Male	88 (48)	11 (52)	26 (53)	16 (48)	18 (39)	17 (50)	0.694
Race							0.891
White	155 (84)	19 (90)	41 (84)	29 (83)	37 (80)	29 (85)	
Black	25 (14)	1 (4.8)	6 (12)	5 (14)	8 (17)	5 (15)	
Other	5 (2.7)	1 (4.8)	2 (4.1)	1 (2.9)	1 (2.2)	0 (0)	
Hispanic ethnicity	95 (51)	11 (52)	26 (53)	23 (68)	15 (33)	20 (59)	0.037
Prehospital variables							
Residence							<0.001
Home	162 (88)	21 (100)	49 (100)	31 (89)	36 (78)	25 (73)	
Skilled-care facility	23 (12)	0 (0)	0 (0)	4 (11)	10 (22)	9 (27)	
ADL dependency count	0 (0–1)	0 (0–0)	0 (0–0)	0 (0–1)	1 (0–4)	2 (1–5)	<0.001
Clinical Frailty Scale score	4 (3–4)	2 (1–2)	4 (3–5)	3 (2–5)	6 (4–6)	6 (6–7)	<0.001
Charlson Comorbidity Index Score	2 (1–4)	1 (0–2)	2 (1–4)	3 (1–5)	3 (2–4)	3 (1–6)	<0.001
ICU variables							
APACHE II Score, mean (SD)	29 (7.8)	27 (6.5)	28 (8.1)	32 (7.7)	27 (7.5)	30 (7.4)	0.01
Type of respiratory support							0.208
Mechanical ventilation	146 (79)	18 (86)	39 (80)	31 (89)	31 (68)	27 (79)	
Non-invasive mechanical ventilation only	39 (21)	3 (14)	10 (20)	4 (11)	15 (33)	7 (21)	
ICU days	5 (3–8)	2 (2–6)	4 (3–7)	8 (4–12)	4 (2–8)	5 (3–9)	0.003
Post-ICU variables							
Post-ICU frailty phenotype score	3 (2–4)	1 (0–2)	3 (2–3)	3 (3–4)	3.5 (3–4)	4 (3–5)	<0.001
Cognitive impairment*	48 (27)	2 (9.5)	6 (13)	11 (31)	0 (0)	29 (100)	0.003
ADL dependency count at hospital discharge	4 (1–5)	0 (0–2)	1 (0–2)	5 (1–5)	5 (3–5)	6 (6–6)	0.0001
Total hospital days	12 (8–21)	9 (5–15)	11 (8–21)	16 (8–26)	13 (9–20)	14 (11–20)	0.1
Discharge location							<0.001
Home	100 (54)	19 (91)	39 (80)	13 (37)	17 (37)	12 (36)	
Long-term acute care	4 (2.2)	0 (0)	1 (2.0)	1 (2.9)	1 (2.2)	1 (2.9)	
Post acute care facility	8 (44)	2 (9.5)	9 (18)	21 (60)	28 (61)	21 (62)	
Died in 6 months	23 (15)	0 (0)	3 (7)	6 (18)	6 (16)	8 (33)	0.001

Data are presented as n (%) or median (IQR) unless otherwise stated. Cognitive impairment assessments were conducted during the baseline assessment on the ward, after the ICU, during the week before hospital discharge. Nine participants with missing cognitive impairment assessment data.
*Cognitive impaired defined as either delirium using the Confusion Assessment Method-ICU or dementia using the Mini-Cog test (score 2).
ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.

frail, chronically physically frail or end-stage frail (subtypes 3–5) (p=0.017). Serum biomarker levels are reported in online supplemental table E4.

Frailty subtype serum exosome proteomic profiles

Among the 45 participants with serum exosome proteomics, differences in demographic characteristics, clinical characteristics and recovery rates by frailty subtype were similar to those observed in the larger cohort (online supplemental table E5 and figure E2). From this sample, we identified 661 serum exosome proteins.

Differential protein expression and protein functional class analyses suggested three groups among the five frailty subtypes consisting of subtype 1, subtype 2 and subtypes 3–5. The number of differentially expressed proteins identified using Limma was greatest when subtypes 1 and 2 were compared with subtypes

3 and 5. There was little or no difference in protein expression comparing subtypes 3, 4 and 5 (figure 4A and online supplemental tables E6–14). Cluster analyses revealed that protein expression segregates to a significant although incomplete extent into groups of subtype 1, subtype 2 and subtypes 3–5 (figure 4B–D). While Limma revealed that subtype 4 had only one and four proteins differentially expressed compared with subtypes 1 and 2, respectively (figure 4A), subtype 4 still segregated mostly with subtypes 3 and 5 in cluster analyses (figure 4B–D). Using frailty subtype 1 as a comparator group, CAMERA revealed differential Reactome protein functional classes primarily related to regulation of immunity, cell replication and gene transcription, and metabolism across subtypes 2, 4, and 5 (online supplemental tables E6–9). No differential Reactome protein functional classes were identified between subtypes 1 and 3. Consistent with our protein expression findings, we did not identify any Reactome
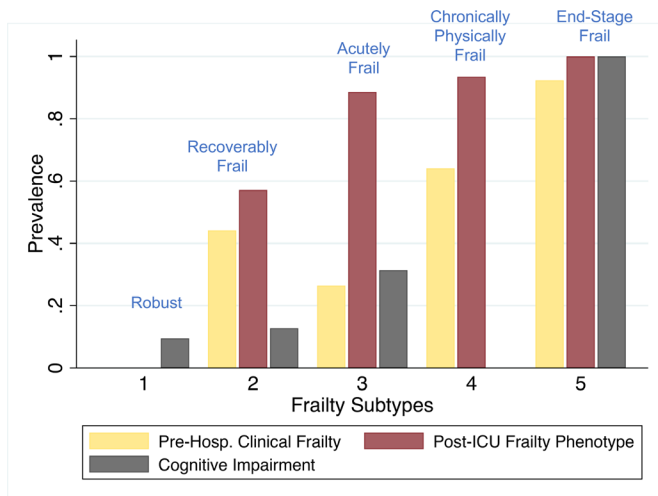
Figure 2 Prevalence of prehospitalisation frailty (Clinical Frailty Score ≥5), the postintensive care unit (ICU) frailty phenotype, and cognitive impairment (based on Confusion Assessment Method (CAM)-ICU and Mini-Cog measured during the week prior to hospital discharge) by frailty subtypes.

protein functional class differences between subtypes 3, 4, and 5 (online supplemental tables E13 and 14).

Analysis of proteins differentially expressed by Limma which belong to the Reactome protein functional classes identified by CAMERA suggest that compared with subtype 1, subtypes 2, 4, and 5 have impaired innate immunity (table 3).
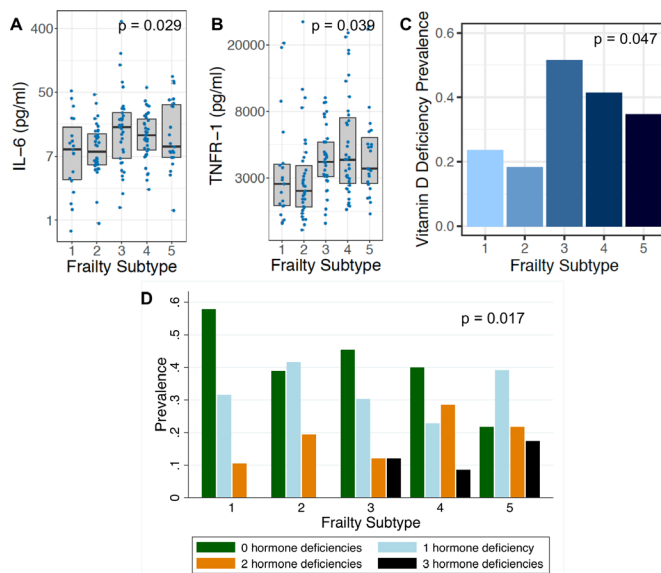
Figure 3 (A) Interleukin-6 (IL-6) and (B) tumour necrosis factor-alpha receptor (TNFR)−1 levels during the week prior to hospital discharge by frailty subtypes. Bars represent median levels, boxes represent IQR, and dots represent individual observations. (C) Prevalence of 25-hydroxy vitamin D deficiency during the week prior to hospital discharge by frailty subtypes. Vitamin D deficiency is defined as<20 ng/mL. (D) Prevalence of the number of hormone deficiencies in either insulin growth factor-1, dehydroepiandrosterone-sulfate, or free testosterone. Hormone deficiency cutoffs were defined as the sex-specific lowest quartile of the study population.

Frailty subtypes, survival and recovery
The unadjusted 6-month survival and basic ADL recovery rates both decreased significantly across increasing frailty subtypes (figure 5). All robust patients (subtype 1) survived and recovered. Among recoverably frail patients (subtype 2), 93% survived and 83% recovered. Acutely frail and chronically physically frail patients (subtypes 3 and 4) had similar 6-month survival and recovery of approximately 80% and 60%, respectively. Among end-stage frail patients (subtype 5), only 67% survived and 45% recovered. In adjusted analyses, there was an additional 42% increase in the 6-month mortality rate across each increasing frailty subtype (adjusted-mortality rate ratio: 1.42, 95% CI 1.03 to 1.94). In adjusted Fine-Gray competing-risk regression analyses, there was an additional 49% decrease in the 6-month ADL recovery rate with each increasing frailty subtype (adjusted recovery rate ratio: 0.51, 95% CI 0.41 to 0.63). Recovery rate ratio effect estimates were nearly identical in the sensitivity analysis (adjusted recovery rate ratio: 0.50, 95% CI 0.40 to 0.63), suggesting that there is no significant time-aggregation bias.

DISCUSSION
Using ARF as a model of accelerated ageing, we applied the geriatric construct of frailty to elucidate five new and meaningfully different subtypes of older ARF survivors. The acutely frail subtype has minimal prehospitalisation frailty and disability and predominantly ICU-acquired frailty and slow recovery, and therefore may be an optimal group for post-ICU physical rehabilitation. The end-stage frail subtype has pre-ICU frailty, post-ICU FP frailty, cognitive impairment, the slowest recovery rate and a 33% 6-month mortality, suggesting that they may benefit from post-ICU palliative care interventions. Frailty subtypes appear phenotypically different based on the degree of their prehospitalisation multimorbidity that is captured with the Clinical Frailty Scale, and post-ICU cognitive impairment. However, the three subtypes with the slowest recovery appear endotypically similar with persistent inflammation, multiple anabolic hormone deficiencies, and impaired innate immunity. While these deficits have been individually reported in adults with acute and protracted critical illness,[43–49] our finding of such profound inflammation and multiple anabolic hormone deficiency that persists after the resolution of critical illness in older adults preparing for hospital discharge suggests that these deficits may be clinically important and potential therapeutic targets in a much larger population of ICU survivors than previously recognised.

Previous frailty research in critical care has focused primarily on identifying prehospitalisation frailty as a risk factor for adverse outcomes.[16 50] The mechanistic underpinnings of frailty in critical care patients has not yet been thoroughly investigated. Since most critical illness is unpredictable, it has not been feasible to enrol patients and make clinical or biological measurements prior to their ICU admission. Our study advances frailty research in critical care by being the first to link clinical measures of frailty with inflammation and anabolic hormone deficiencies, common mechanisms governing age-related frailty that are driven to extreme levels by critical illness, and that might underlie the pathobiology of frailty-related physical impairment after ARF. To do this, we focused on ICU survivors; we performed frailty assessments on the medical ward near the time of hospital discharge when delirium or cognitive function may be milder, which in turn, allowed us to make measures of grip strength and gait speed[2]; and we estimated the 1-month prehospitalisation Duke Activity Status Index as the frailty domain of physical activity.[17]

Count of differentially expressed proteins between frailty subtypes
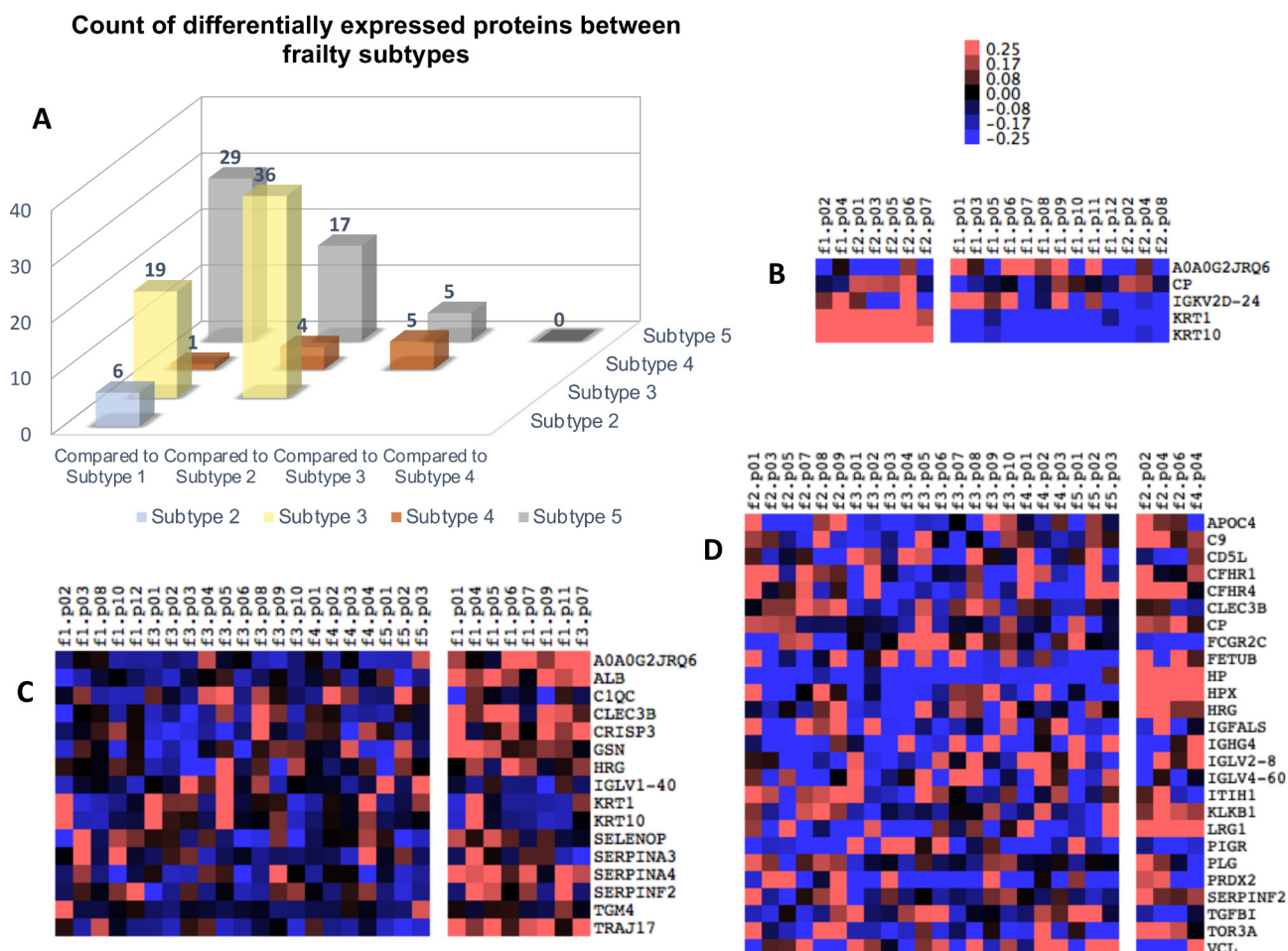
Figure 4 (A) Count of differentially expressed proteins between frailty subtypes using Limma at p<0.05 with FDR<0.2 and an absolute $\log_2$ fold change of >0.2. Specific protein names are listed in online supplemental table E6–14. Heatmaps of unsupervised cluster analyses of differentially expressed proteins between (B) frailty subtypes 1 versus 2, (C) frailty subtypes 1 versus 3–5, and (D) frailty subtypes 2 versus 3–5. Numbers in the colour legend represent $\log_2$ concentration (scale arbitrary), mean centred by protein. Individual patients are listed in columns with f# denoting the frailty subtype number and p# representing patient study identification number. Names of differentially expressed proteins are listed in the rows. Heatmaps suggest that there is significant although incomplete segregation of protein expression into three groups consisting of subtype 1, subtype 2 and subtype 3–5.

Accordingly, our measure of post-ICU frailty represents the cumulative effects of deficits that were present prior to critical illness and those acquired during critical illness.

Our finding of greater inflammation at hospital discharge in frailty subtypes with slower recovery supports the hypothesis that critical illness leads to persistent inflammation, immunosuppression and catabolic syndrome in many ICU survivors, not just those with chronic critical illness.[51] Our findings are consistent with studies that identified associations between inflammation at hospital discharge and increased 1-year mortality in pneumonia survivors,[52] and inflammation at 3 months after ICU hospitalisation and worse mobility in ARF survivors.[47] Since we measured inflammation just prior to hospital discharge, we cannot discriminate between prehospitalisation inflammation related to pre-existing frailty and persistent inflammation due to ARF. However, the mean (SD) IL-6 level among study participants was 23 (46) pg/mL, which is 5–10 times greater than in frail community-dwelling older adults.[24 53 54] Therefore, we expect that most inflammation observed in ARF survivors stems from critical illness.

Table 3 Serum exosome proteins differentially expressed that belong to Reactome functional protein classes identified by CAMERA

	Subtype 1 versus 2	Subtype 1 versus 3	Subtype 1 versus 4	Subtype 1 versus 5
Differentially expressed proteins	KRT1	No Reactome classes identified to compared with differentially expressed proteins	IGKV4-1	CLU, CRP, C4B, LCN2, TF
Reactome protein functional classes identified with CAMERA (direction of regulation)	Innate immune system (*down*)	No Reactome classes identified	Triggering of complement (*down*), creation of C4 and C2 activators (*down*)	Complement cascade (*down*), cytokine signalling in immune system (*up*), membrane trafficking (*up*)

CAMERA, Correlation Adjusted Mean Rank gene set test.
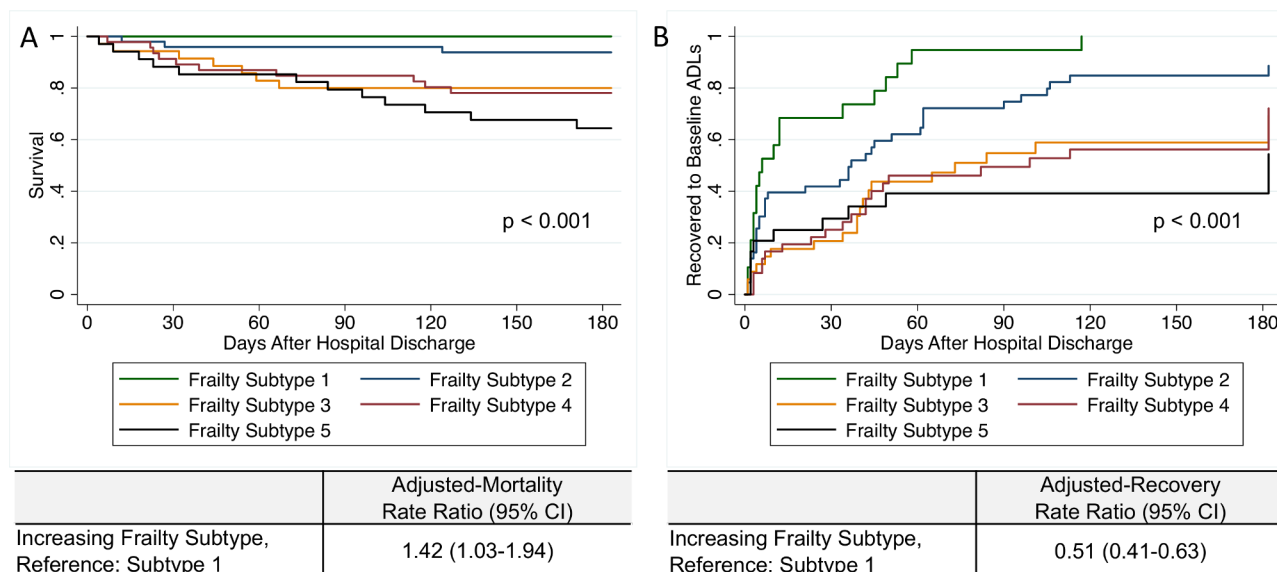
Figure 5 (A) Kaplan-Meier survival function plot of frailty subtypes, showing 6-month survival from hospital discharge. Mortality rate ratios are HRs estimated from Cox proportional hazards models. (B) Kaplan-Meier failure function plot of frailty subtypes showing recovery to prehospitalisation basic activities of daily living (ADLs) independence within 6 months after hospital discharge. Recovery rate ratios are estimated from Fine-Gray survival regression models. Mortality ratio ratios and recovery rate ratios are adjusted for age, sex, pre-existing ADL disability, Charlson Comorbidity Index score, and Acute Physiology and Chronic Health Evaluation II score.

Three landmark case series of prolonged mechanical ventilation patients have shown depression of the neuroendocrine axes during the ICU stay.[43–45] Our finding of multiple anabolic hormone deficiencies in a large proportion of older adult ARF survivors just prior to hospital discharge suggests that post-critical illness anabolic hormone suppression, whether pre-existing and/or ICU acquired, may be more widespread, severe and persistent than previously recognised. In community-dwelling older adults, the number of anabolic hormone deficiencies in free-testosterone, DHEA and IGF-1 predict frailty and mortality better than any single anabolic hormone deficiency,[32 55] which has led investigators to propose multiple low-dose anabolic hormone replacement therapy for frail older adults.[33 56] Since we observed multiple anabolic hormone deficiencies in frailty subtypes with the slowest recovery, future studies should investigate whether multiple anabolic hormone deficiencies after critical illness represent a therapeutic target for improving physical recovery. While our sex-specific lowest study population quartile definition for anabolic hormone deficiency follows the approach used in landmark ageing studies,[32 33] it is arguably arbitrary. However, these lowest quartile levels are lower than deficiency levels defined for adults in the outpatient setting. Applying the DHEAs cut-off of <15th percentile for young men and women that was used in a landmark DHEA supplementation trial of older adults,[57] 98% of men and 100% of women in our study would be deficient. Applying the LCMS-derived total testosterone cut-off for symptomatic hypogonadism in older men of <3.2 ng/mL,[58] 83% of men in our study would be deficient. Applying the <2.5th age-adjusted and sex-adjusted percentile for IGF-1,[59] a cut-off used to identify growth hormone deficient patients,[60] 27% of men and 20% of women in our study would be deficient.

Our study has additional limitations. Our results need to be externally validated in a cohort that also includes younger adult ARF survivors. While we excluded those with severe dementia, our measures of cognitive impairment after the ICU cannot differentiate more mild pre-existing cognitive impairment from ICU-acquired cognitive impairment. Furthermore, the Mini-cog does not pedict long-term cognitive impairment in ARDS survivors.[61] Future studies should use more robust measures of cognitive function, such as those used in the ALTOS or BRAIN-ICU cohort studies,[62 63] which may allow for better discrimination of subtypes. Our assessment of physical activity in the month prior to hospitalisation is susceptible to mismeasurement. However, other studies support that recall and surrogate response bias of physical activity in ICU survivors is minimal,[64–66] and we previously showed that the DASI has high construct and predictive validity in ARF survivors.[17] We estimated mortality and recovery rate ratios for each increasing frailty subtype while controlling for severity of illness with the APACHE-II score, but we did not control for daily sequential organ failure assessment scores. We assessed serum exosome proteomics because prior frailty-related plasma proteomic profiling in community-dwelling older adults was unrevealing,[67] and because serum exosomes are involved in relevant pathobiological functions of organs affected by critical illness stressors.[68] However, serum exosome proteomic profiling remains a new field, and our results should be considered exploratory. Recent advances in plasma proteomic profiling techniques have led to identification of plasma proteomic signatures of age in healthy humans.[69] Therefore, using plasma proteomics to assess multisystemic dysregulation in ARF survivors should be reconsidered. We did not assess for impaired muscle mitochondrial bioenergetics, an additional mechanism of age-related frailty that has been implicated in ICU-acquired weakness.[70–72]

In summary, we identified five different frailty subtypes, that if validated, could help identify patient subgroups that may maximally benefit from targeted post-ICU rehabilitation or palliative care. Combined physical and cognitive rehabilitation, which has been shown to be feasible in ICU survivors,[73] could be considered in those subtype patients who have both new disability and cognitive impairment at hospital discharge. Consistent with complexity underlying frailty, no single biological frailty deficit appears to dominate any single frailty subtype. Instead, multiple frailty subtypes with the slowest recovery and highest mortality

all appear to have a combination of persistent inflammation, multiple anabolic hormone deficiencies and immunosuppression. Our observation that an acutely frail ARF survivor subtype appears to have inflammation and anabolic hormone deficiencies at hospital discharge similar to subtypes with chronic physical frailty or end-stage frailty supports the hypothesis that the critical illness of ARF accelerates age-related frailty mechanisms in older adults. Our findings suggest that a systems biology approach to further understand the multisystemic dysregulation that persists after ARF may be very revealing and supports the hypothesis that post-ICU therapeutic interventions may need to target multiple deficits simultaneously in order to successfully improve recovery after critical illness.

Author affiliations
[1]Pulmonary, Allergy, and Critical Care, Columbia University Irving Medical Center, New York, New York, USA
[2]Medicine, University of Washington School of Medicine, Seattle, Washington, USA
[3]Bioinformatics, Columbia University Irving Medical Center, New York, New York, USA
[4]Outcomes After Critical Illness and Surgery Group, Johns Hopkins University, Baltimore, Maryland, USA
[5]Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[6]Department of Biostatistics, Johns Hopkins University—Bloomberg School of Public Health, Baltimore, Maryland, USA
[7]Cardiology, Columbia University Irving Medical Center, New York, New York, USA
[8]Regeneron Pharmaceuticals, Tarrytown, New York, USA

Twitter David J Lederer @davidlederer

ORCID iDs
Matthew R Baldwin http://orcid.org/0000-0003-4670-3433
Dale M Needham http://orcid.org/0000-0002-9538-0557
David J Lederer http://orcid.org/0000-0001-5258-0228

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