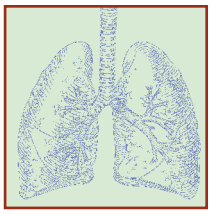

Identifying Comorbid Subtypes of Patients With Acute Respiratory Failure

By Kelly M. Potter, PhD, RN, CNE, Heather Dunn, PhD, ACNP-BC, ARNP, Anna Krupp, PhD, RN, Martina Mueller, PhD, Susan Newman, PhD, RN, CRRN, Timothy D. Girard, MD, MCSI, and Sarah Miller, PhD, RN

Background Patients with acute respiratory failure have multiple risk factors for disability following their intensive care unit stay. Interventions to facilitate independence at hospital discharge may be more effective if personalized for patient subtypes.

Objectives To identify subtypes of patients with acute respiratory failure requiring mechanical ventilation and compare post–intensive care functional disability and intensive care unit mobility level among subtypes.

Methods Latent class analysis was conducted in a cohort of adult medical intensive care unit patients with acute respiratory failure receiving mechanical ventilation who survived to hospital discharge. Demographic and clinical medical record data were collected early in the stay. Clinical characteristics and outcomes were compared among subtypes by using Kruskal-Wallis tests and χ^2 tests of independence.

Results In a cohort of 934 patients, the 6-class model provided the optimal fit. Patients in class 4 (obesity and kidney impairment) had worse functional impairment at hospital discharge than patients in classes 1 through 3. Patients in class 3 (alert patients) had the lowest magnitude of functional impairment ($P<.001$) and achieved the earliest out-of-bed mobility and highest mobility level of all subtypes ($P<.001$).

Conclusions Acute respiratory failure survivor subtypes identified from clinical data available early in the intensive care unit stay differ in post–intensive care functional disability. Future research should target high-risk patients in early rehabilitation trials in the intensive care unit. Additional investigation of contextual factors and mechanisms of disability is critical to improving quality of life in acute respiratory failure survivors. (*American Journal of Critical Care.* 2023;32:294-301)

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More than 1 million patients admitted annually to intensive care units (ICUs) in the United States require mechanical ventilation for acute respiratory failure (ARF).[1] Advances in critical care have resulted in decreased mortality rates for ARF, leading to a growing number of survivors.[2] However, up to 65% of these survivors experience significant functional disability, which negatively affects quality of life and can persist for years following the ARF hospitalization.[3-7] Despite clear evidence that functional disability is a common problem for ARF survivors, early identification and management remain infrequently studied and poorly understood.

Interventions designed to improve post-ICU physical function have been examined in a number of clinical trials, with some demonstrating improvement in function[8-13] and others having neutral results.[14-16] The inconsistent response to early mobilization interventions in the ICU may be explained, in part, by patient heterogeneity.[17] Accordingly, the identification and study of distinct subtypes of patients with ARF may reveal opportunities for targeted early rehabilitative interventions that maximize benefit and reduce the burden of functional disability after intensive care. Although several independent risk factors associated with functional disability after intensive care have been identified,[18-20] a single risk factor, such as mechanical ventilation itself, is unlikely to uncover subtypes of patients most likely to benefit from rehabilitative interventions in the ICU. Therefore, the purposes of this study were to (1) use electronic health record (EHR) data to identify comorbid subtypes of patients with ARF who required mechanical ventilation and survived their hospitalization and (2) determine which comorbid subtypes are at greatest risk for functional disability at hospital discharge.

About the Authors

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Methods

Setting and Sample

We conducted this retrospective, single-center cohort study of ICU patients receiving mechanical ventilation by using University of Iowa Hospitals and Clinics EHR data. The study was approved by the institutional review board of the University of Iowa (#202002377).

We included patients who were admitted directly to the medical ICU between October 3, 2016, and December 31, 2019; required mechanical ventilation for at least 24 hours; had an ICU stay of at least 48 hours; and were discharged from the hospital alive. We excluded patients if they did not receive mechanical ventilation within the first 7 days of ICU admission, had a primary diagnosis or history of neuromuscular disorder or cerebrovascular accident, had an existing tracheostomy, had an amputation of a lower limb, or were pregnant or postpartum.

Every year, more than 1 million patients admitted to ICUs in the United States require mechanical ventilation for acute respiratory failure, a highly heterogeneous condition.

Latent Class Analysis Candidate Variables

From a thorough literature search on potential risk factors for poor long-term outcomes after critical illness, we identified baseline demographics, anthropometry, the Charlson Comorbidity Index, clinical characteristics, and treatments present when mechanical ventilation was initiated and during the first 7 days of the ICU stay as initial variables in the latent class analysis. Clinical characteristics included vital signs, laboratory test results, Glasgow Coma Scale score, Riker Sedation-Agitation Scale score, and ventilator settings in the 24 hours surrounding the initiation of mechanical ventilation. Titratable medications (eg, vasopressors, sedatives, benzodiazepines, continuous opioids,

neuromuscular blockers, and insulin) administered during the first 7 days of the ICU stay were defined as dichotomous variables (yes or no). See Supplemental Table 1 (available online only at www.ajcconline.org) for additional details.

Outcomes

The primary outcome was percentage of functional impairment at hospital discharge, a conversion from the total score on the Activity Measure for Postacute Care (AM-PAC).[21] The AM-PAC Inpatient Basic Mobility Short Form allows clinicians to assess difficulty in the execution of 6 tasks: turning over in bed, moving from lying on the back to sitting on the side of the bed, moving from a bed to a chair and back, sitting down in and standing up from a chair, walking in a hospital room, and climbing 3 to 5 steps with a railing.[21] To determine functional disability at hospital discharge, we converted the final measured score on the AM-PAC Inpatient Basic Mobility Short Form during the last physical therapy consultation of the hospitalization to percentage of functional impairment by using a conversion table.[21] We examined nursing documentation to determine the highest level of mobility in the ICU (defined as lying on the bed, dangling legs over side of bed, standing, sitting in a chair, or walking).

We examined differences in percentage of functional impairment, which was converted from the AM-PAC total score.

Data Analyses

We used latent class analysis to classify patients into comorbid subtypes based on demographic and clinical characteristic data collected during the first 7 days of the ICU stay. Latent class analysis is a person-centered approach to clustering that uses a mixture model to identify patient subtypes that are not directly observable.[22] Latent class analysis has several advantages over other clustering methods because it does not require normally distributed variables, variables can be of varying levels of measurement, and covariates can be included in model development.[23,24] Following expert recommendations for latent class analysis, we managed missing data by using full information maximum likelihood, which uses both complete and incomplete data to estimate model parameters.[24]

In the initial analysis, we estimated all possible models including from 1 through 6 hypothesized patient clusters.[25] We selected this range of clusters because previous studies identified 2 subtypes[26] and 3 subtypes[27] of patients with acute respiratory distress syndrome, and testing models with additional clusters could account for further heterogeneity in subtypes of patients with ARF not related to acute respiratory distress syndrome. We used a backward stepwise method for variable inclusion in the final latent class analysis model (prespecified threshold for removal: $P > .05$, R^2 loadings < 0.10). We entered sex and primary diagnosis category in the latent class model as inactive covariates to allow assessment of the relationship with the latent classes without influencing model parameter estimates.[25] We determined model fit by using local fit statistics (Wald χ^2 test, R^2 loadings, and bivariate residuals) and global fit statistics (Bayesian information criterion, proportion of classification errors, entropy R^2 statistics, and the Vuong-Lo-Mendell-Rubin likelihood ratio). Details of the latent class analysis procedure are provided in a multipage Supplement (available online only at www.ajcconline.org).

We used Kruskal-Wallis tests and χ^2 tests of independence to compare demographic and clinical characteristics during the ICU stay, functional disability at hospital discharge, and mobility level in the ICU between subtypes. We presented data using medians (IQRs) and frequencies (percentages). Data were analyzed with SPSS Statistics 27 (IBM), Latent Gold 6.0 (Statistical Innovations), and Python 3.10 (Python Software Foundation).

Results

General Results

Of 1082 potential patient encounters, we excluded 148, most commonly because they were second hospital encounters requiring medical ICU admission (Figure 1). The final sample included 934 medical ICU patients with a median (IQR) age of 60 (48-68) years. Of these, 513 patients (54.9%) were male, and 644 (69.0%) lived at home before their ICU admission (Supplemental Table 2, available online only).

The median (IQR) Glasgow Coma Scale score on admission was 7 (4-11). The median (IQR) Riker Sedation-Agitation Scale score in the 24 hours following initiation of mechanical ventilation was 3.0 (2.2-3.4). Within the sample during the first 7 days of their ICU admission, 263 patients (28.2%) were in a coma (Riker Sedation-Agitation Scale score of 1) at some point, and 364 (39.0%) received vasopressors (Supplemental Table 3, available online only).

Latent Class Analysis

The 6-class model provided the optimal fit. Table 1 displays a summary of model fit statistics

for 1-class through 6-class models once only final model variables remained. The 6-class model had the lowest Bayesian information criterion and highest-entropy R^2, indicating adequate class prediction. Average latent class probabilities for classes 1 through 6 were 0.96, 0.93, 0.95, 0.86, 0.91, and 0.93, respectively. Bivariate residuals between model variables were less than 3.84, indicating good local fit (Supplemental Table 4, available online only). The variables included in the final model and direct effects specified between variables are presented in Supplemental Table 1 (available online only).

Characteristics of Comorbid Groups

The 6 subtypes had several statistically and clinically significant similarities and differences in demographic and clinical characteristics. Overall, the groups were similar in age. The groups differed in diagnoses, body mass index, level of consciousness (Glasgow Coma Scale score), sedation level (Riker Sedation-Agitation Scale score), sedative use, vasopressor use, physiologic parameters (eg, vital signs and laboratory test results), and time to initiation of mechanical ventilation (Supplemental Tables 5 and 6, available online only).

As shown in the Supplemental Figure and Supplemental Table 5 (each available online only), the 6 subtypes can be described qualitatively as follows: class 1, overweight patients with limited use of vasopressors and respiratory support (typical respiratory failure, n = 367 [39.3%]); class 2, patients with few comorbidities but high respiratory support needs (acute respiratory demands, n = 220 [23.6%]); class 3, patients alert on admission with low sedation burden and minimal vasopressor needs (awake and stable, n = 113 [12.1%]); class 4, patients with obesity and severe kidney impairment (n = 105 [11.2%]); class 5, patients with a low level of consciousness on admission, moderate leukocytosis, severe kidney impairment, and hyperglycemia (metabolic alterations, n = 72 [7.7%]); and class 6, patients who were overweight, were alert on admission, and had a long duration from ICU admission to initiation of mechanical ventilation (late decline, n = 57 [6.1%]).The 6 subtypes are described as classes 1 through 6 henceforth.

Association Between Comorbid Subtypes and Outcomes

Percentage of Functional Impairment at Hospital Discharge. As shown in Table 2 and Figure 2, functional impairment at hospital discharge was more severe in patients in class 4 than in patients in class 1 ($P = .01$), class 2 ($P = .004$), and class 3 ($P < .001$). Patients in class 3 had the lowest magnitude of functional impairment at hospital discharge, significantly less than patients in classes 4 and 5 (Figure 2).

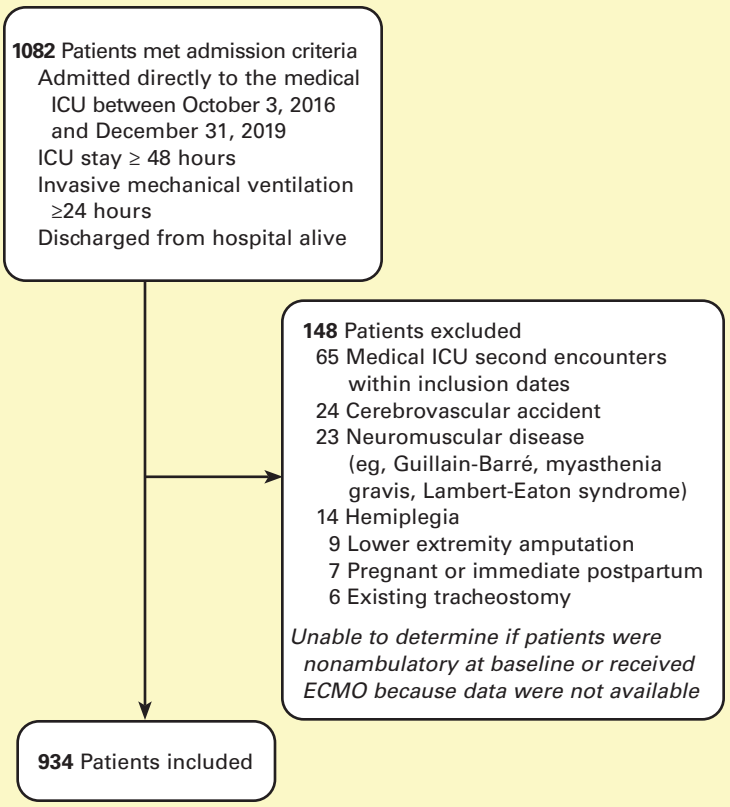

Figure 1 Selection of patients for inclusion in the study.

Abbreviations: ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

Table 1
Model fit statistics[a]

No. of classes	BIC	Classification errors	Reduction in errors	Entropy R^2	VLMR
1	40481.3641	0.0	1.0	1.0	
2	38325.8978	0.0574	0.8781	0.7989	0.0000
3	37136.8417	0.0706	0.8770	0.8203	0.0000
4	35481.8032	0.0844	0.8568	0.8335	0.0000
5	35369.2212	0.0937	0.8415	0.8388	0.0005
6[b]	34740.9647	0.0697	0.8890	0.8844	0.0000

Abbreviations: BIC, Bayesian information criterion; VLMR, Vuong-Lo-Mendell-Rubin likelihood ratio.

[a] The lowest BIC was used as the primary criterion for determining the correct model of subtypes because it is one of the most reliable criteria for determining the correct number of subtypes. Entropy R^2 is a pseudo R^2 statistic that indicates how well one can predict class memberships on the basis of variables and covariates; the closer these values are to 1, the better the class prediction. VLMR likelihood ratio tests whether k classes provide improved model fit compared with the $k-1$ class model.

[b] Final model.

Table 2
Outcomes by comorbid subtype (N=934)[a]

Outcome	Class 1 (n=367)	Class 2 (n =220)	Class 3 (n=113)	Class 4 (n=105)	Class 5 (n=72)	Class 6 (n=57)	*P*
Functional impairment, %	47.0 (21.0-69.0)	47.0 (11.0-73.0)	36.0 (11.0-54.0)	54.0 (36.0-81.0)	51.0 (36.0-81.0)	51.0 (21.0-81.0)	<.001[b]
Days from admission to AM-PAC	7.0 (4.0-12.0)	9.0 (5.0-14.5)	7.0 (4.0-12.0)	11.0 (7.0-15.0)	11.0 (6.0-15.0)	13.0 (7.0-22.0)	<.001[b]
Duration of MV, d	2.3 (1.6-4.1)	3.1 (1.9-5.7)	3.5 (2.3-7.2)	2.7 (1.7-5.6)	2.8 (2.0-3.9)	4.5 (2.7-10.0)	<.001[b]
ICU LOS, d	4.8 (3.3-6.9)	5.7 (3.9-8.9)	4.5 (3.2-7.3)	6.1 (4.3-8.9)	5.2 (4.2-7.7)	9.1 (5.9-12.9)	<.001[b]
Hospital LOS, d	8.0 (5.0-14.0)	10.5 (7.0-16.5)	12.0 (8.0-18.0)	13.0 (8.0-19.0)	13.0 (9.0-18.0)	18.0 (10.0-28.5)	<.001[b]
Highest level of ICU mobility							<.001[c]
Lying in bed or dangling legs	89 (24.3)	49 (22.3)	8 (7.1)	23 (21.9)	24 (33.3)	14 (24.6)	
Standing, sitting in chair, or walking	278 (75.7)	171 (77.7)	105 (92.9)	82 (78.1)	48 (66.7)	43 (75.4)	
Ambulation in ICU							<.001[c]
Did not walk	232 (63.2)	147 (66.8)	56 (49.6)	79 (75.2)	58 (80.6)	39 (68.4)	
Walked	135 (36.8)	73 (33.2)	57 (50.4)	26 (24.8)	14 (19.4)	18 (31.6)	
Days to first OOB mobility	3.2 (2.1-4.8)	3.7 (2.6-5.9)	1.2 (0.6-1.8)	4.0 (2.3-6.6)	4.1 (3.1-5.7)	3.1 (1.4-6.0)	<.001[b]

Abbreviations: AM-PAC, Activity Measure for Postacute Care Inpatient Basic Mobility Short Form measurement; ICU, intensive care unit; LOS, length of stay; MV, mechanical ventilation; OOB, out-of-bed.

[a] Values are expressed as median (IQR) or number (percentage).
[b] Difference among 6 groups determined by Kruskal-Wallis test.
[c] Difference among 6 groups determined by χ^2 test of independence.

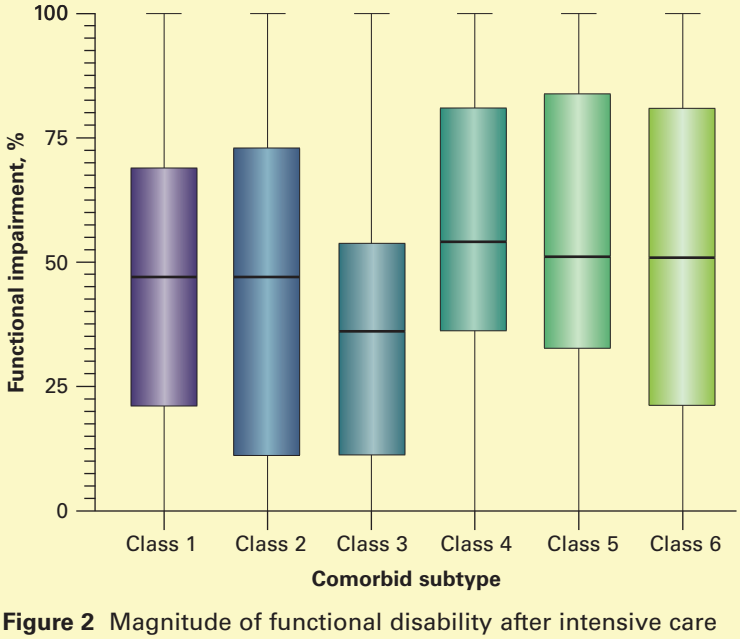

Figure 2 Magnitude of functional disability after intensive care among subtypes. The comorbid subtypes differed in severity of functional impairment at hospital discharge. Severity of functional impairment (ranging from 0% impaired to 100% impaired) was a conversion from the last Activity Measure for Postacute Care sum score, which was obtained by trained physical therapists at the last physical therapy consultation of the hospitalization. Patients in class 3 had the least severe functional impairment at hospital discharge. Patients in class 4 and class 5 had the worst functional impairment at hospital discharge.

Mobility Level. During the ICU stay, 105 of the patients in class 3 (92.9%) achieved out-of-bed mobility, a percentage greater than that in all other classes (Table 2; $P<.001$). A higher percentage of patients in class 3 than in classes 2, 4, and 5 walked in the ICU ($P<.001$). Patients in class 3 had the earliest out-of-bed mobility compared with all other subtypes ($P<.001$).

Discussion

In this study involving nearly 1000 medical ICU patients receiving mechanical ventilation, we identified 6 comorbid subtypes using EHR data available early in the ICU stay. These subtypes exhibited differences in functional disability at hospital discharge and mobility level in the ICU, suggesting that our method of class identification may identify patients at greatest need for early mobilization interventions and directed post-ICU rehabilitation.

In prior work, we explored patient-level and environmental barriers (eg, poor staffing and high workload) that contribute to poor delivery of interventions, such as early mobilization, aimed at preventing functional disability after intensive care.[28,29] Dedicated mobility personnel promote patient mobility in the ICU, but many institutions

do not have the money or staff needed to add specialized employees. One way to mitigate these barriers is to allocate scarce resources to the patients who would benefit most from early mobilization. The interprofessional ICU team can optimize and coordinate care through daily planning discussions that identify patients at highest risk for functional disability and strategically plan mobilization sessions.[30] Bedside nurses can mobilize lower-risk patients,[31] allowing physical, occupational, and respiratory therapists to direct their expertise to those at highest risk. Research on the heterogeneity of treatment effects in early mobilization can guide such resource allocation by determining which patient groups will benefit most from rehabilitative interventions.

To our knowledge, 6 previous studies have examined subtypes of disability outcome,[32] trajectory,[33,34] risk,[35,36] or frailty[37] in ICU survivors, each using a different approach. Compared with these studies, our cohort was the largest and the first to use only clinical data available early in the ICU stay. One previous study used plasma biomarkers,[36] 1 classified patients according to frailty domains,[37] and 4 relied on discharge characteristics (eg, length of stay and health status after discharge)[32,35] or trajectories[33,34] when identifying classes. Because we used only variables that were available around the time that mechanical ventilation was initiated, our method has high clinical utility, facilitating early identification of patients at high risk for functional disability. Future work in this area could investigate the feasibility of classifying patients in real time through predictive analytics to assign latent class membership to patients using the candidate predictors.[27]

Although our primary purpose was not to identify individual risk factors for functional disability after intensive care, our results suggest that obesity and metabolic alterations should be examined in future mechanistic research because body mass index was higher in patients in class 4—which had the worst functional outcomes—than in patients in classes 1 and 2. Patients with obesity may be at increased risk for functional decline due to muscle catabolism associated with inflammatory mediator secretion by adipose tissue.[38-40] Researchers in 2 studies examined the role of obesity in muscle atrophy during critical illness and concluded that preservation of lean muscle mass and strength during critical illness among patients with overweight or obesity may be explained by energy utilization: adipose tissue may be preferentially used as an energy source in patients with overweight or obesity, whereas muscle tissue is used as an energy source in patients with a healthy weight.[41,42] Further study of the role of obesity in functional disability after intensive care is warranted because approximately one-third of patients in the critical care setting present with obesity.[43]

Kidney impairment was also common in patients in class 4 and class 5; these patients also had significant functional impairment at hospital discharge. Muscle atrophy is a known complication of chronic kidney disease,[44] but acute kidney injury has not been clearly linked with muscle atrophy or weakness. One potential explanation is the role of acid-base alterations in functional disability after intensive care. Acute kidney injury is associated with metabolic acidosis, which perpetuates the ubiquitin-proteasome pathway and induces muscle breakdown.[45] We also found significantly higher blood glucose levels in patients in class 5 than in other classes. Tight glycemic control has been associated with a reduced incidence of ICU-acquired weakness,[46] including when glycemic control is combined with early mobilization.[47]

This cohort was the largest and the first to use only clinical data available early in the ICU stay, which may facilitate early identification of patients at high risk for functional disability.

Practice factors associated with functional disability after intensive care also differed across the comorbid subtypes. Patients in class 3 arrived at the medical ICU with a high level of consciousness and remained more alert in the 24 hours following initiation of mechanical ventilation than patients in all other classes. Light sedation may have allowed for better involvement in early mobilization and other cognitive rehabilitation activities,[28,29] as class 3 had the highest percentage of patients who achieved any out-of-bed mobility or walked in the ICU. We were not able to infer the mobility contextual factors (eg, intensity, timing, frequency, or duration) or environmental factors (eg, staffing, workload, or clinician education) that were associated with functional disability. Further study of these factors and the onset and development of functional disability after intensive care are needed.

Strengths, Limitations, and Future Work

Our study had several strengths. To our knowledge, this study was the first to include both demographic and clinical characteristics present early in the ICU stay to classify patients into comorbid subtypes and determine their differences in functional

disability after intensive care. Our sample size was sufficient to adequately power the latent class and group difference analyses.[48,49] We also derived our model and outcome variables from the EHR, which has pragmatic utility.

This retrospective, single-center study has several limitations, one being a lack of external validation. However, dissemination of these hypothesis-generating results demonstrates proof of concept in the method of applying latent class analysis to EHR data and allows rapid validation of this work in other centers, both in our research group and others. The EHR data we used may have included inaccuracies and provided no measure of preexisting functional status or in-hospital delirium, important predictors of post-ICU functional impairment. Because the focus of this study was to identify subtypes of patients with ARF who survive and may benefit from targeted early rehabilitative interventions, we analyzed ARF survivors only. The current evidence suggests that early mobility interventions in the ICU do not improve survival,[8-11,13-16] but it is possible that our focus only on survivors could influence the reproducibility of ARF subtypes in future cohorts. We were also able to address only the activity domain of disability with 1 measure that had not previously been used as an outcome measure of disability following critical illness. However, the AM-PAC has been validated with the Functional Independence Measure and has accuracy in determining discharge destination and ongoing rehabilitative needs.[50,51] We studied functional disability only at hospital discharge. Patients with functional disability following critical illness experience different trajectories of recovery, and this outcome may also differ among subtypes.

Clinical staff can allocate scarce rehabilitation resources to patients at high risk for disability through care coordination and early planning discussions.

Conclusions

Six ARF survivor subtypes identified from EHR data available early in the ICU stay exhibited differences in functional disability after intensive care and ICU mobility level. Future research should consider targeting patients in class 4 and class 5 in trials of interventions, such as early mobilization, intended to reduce functional disability at hospital discharge. Additional investigation of the onset and trajectory of disability in ARF survivor subtypes and physiological mechanisms of disability in subtypes that may be targets for new interventions is critical to improving understanding of functional disability after intensive care, reducing its burden, and promoting quality of life in survivors of critical illness.

FINANCIAL DISCLOSURES
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SEE ALSO

For more about acute respiratory failure, visit the *Critical Care Nurse* website, **www.ccnonline.org**, and read the article by Fusi et al, "Awake Prone Positioning in Nonintubated Patients With Acute Hypoxemic Respiratory Failure" (February 2023).

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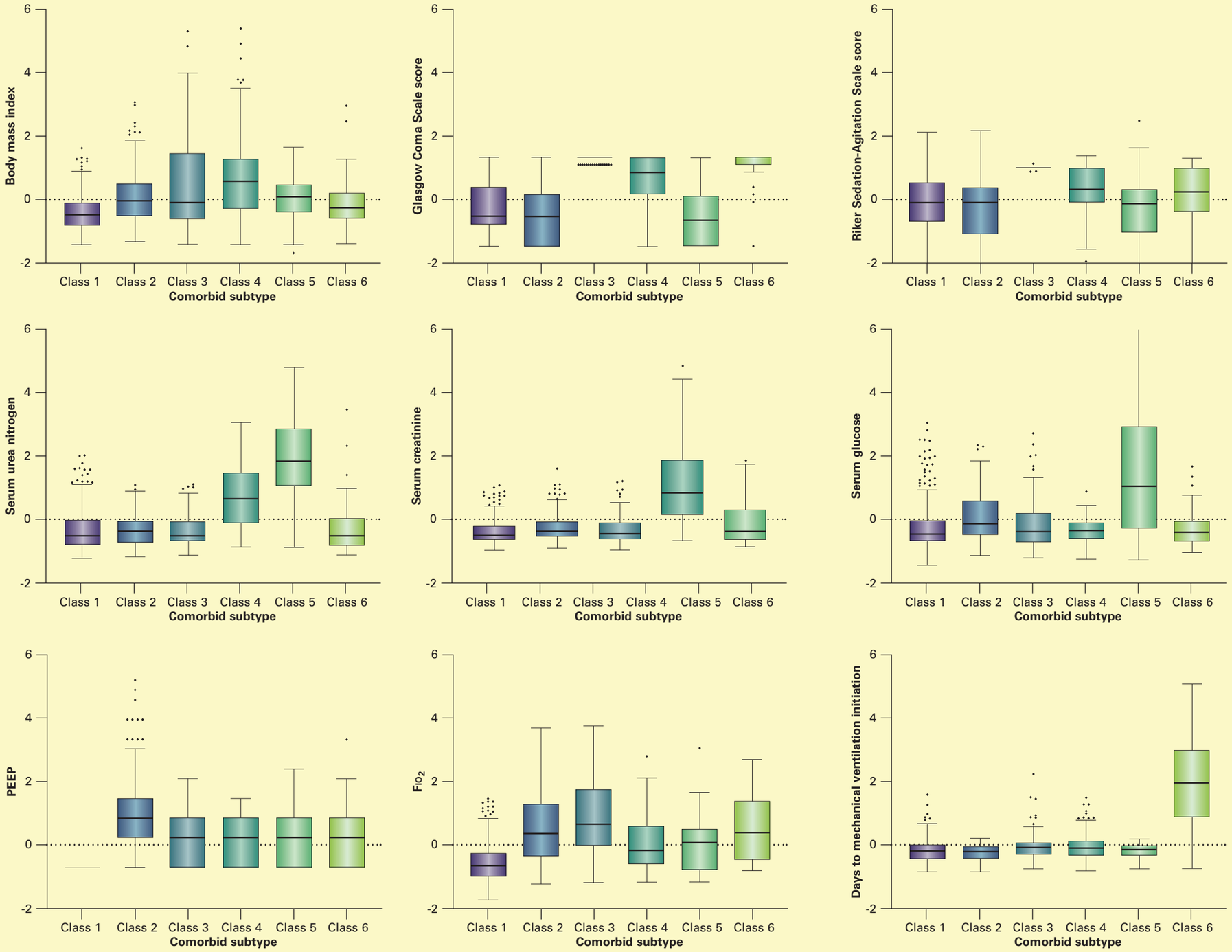

Supplemental Figure Latent class profile between comorbid subtypes. The variables that differentiated the subtypes in the final latent class model were body mass index (calculated as weight in kilograms divided by height in meters squared), Glasgow Coma Scale score on admission; mean Riker Sedation-Agitation Scale score in the first 24 hours after mechanical ventilation initiation; mean serum urea nitrogen, creatinine, and glucose levels in the 24 hours surrounding mechanical ventilation initiation; first positive end-expiratory pressure (PEEP) setting of the first ventilator episode; mean fraction of inspired oxygen (FIO_2) in the first 24 hours of the first ventilator episode; and days from intensive care unit admission to mechanical ventilation initiation. For each graph, the x-axis indicates the comorbid subtype and the y-axis depicts the scaled distributions of model variables, with the mean of the observed values as 0 and the SD as 1.

Supplemental Table 1
Indicators in latent class model development

Indicator entered	% Missing	Wald statistic	*P*	Removal/direct effects[a]
Demographics				
Sex	0			*Covariate*
Race	0	0.77	>.99	Nonsignificant
BMI[b]	18	92.3	<.001	Direct effect: PEEP
Marital partner[c]	0	9.92	.45	Nonsignificant
Living arrangement[d]	0	34.27	.003	R^2<0.10
Insurance status	0	53.77	<.001	R^2<0.10
English as primary language	0	1.49	.91	Nonsignificant
Diagnosis category	0			*Covariate*
CCI total score	0	165.71	<.001	R^2<0.10
Age	0			*Included in CCI total score*
GCS score[e]	0	2201.13	<.001	Direct effect: BUN; days to MV initiation; Riker SAS
Vital signs[f]				
Temperature	1.2	6.72	.24	Nonsignificant
Heart rate	0.6	38.33	<.001	R^2<0.10
Respiratory rate	0.6	66.76	<.001	R^2<0.10
Blood pressure (mean arterial)	3.7	180.35	<.001	R^2<0.10
Oxygen saturation	0.6	233.00	<.001	R^2<0.10
Riker SAS score[g]	1.1	1138.07	<.001	Direct effect: GCS
Continuous infusions[h]				
Vasopressors				
No. of different pressors	0	722.48	<.001	BVR>3.84 with F_{IO_2}
Ever received norepinephrine	0			BVR>3.84 with F_{IO_2}
Ever received vasopressin	0	10.47	.06	Nonsignificant
Ever received epinephrine	0	3.33	.65	Nonsignificant
Ever received phenylephrine	0	6.62	.25	Nonsignificant
Ever received dopamine	0	1.76	.88	Nonsignificant
Ever received dobutamine	0	9.86	<.001	R^2<0.10
Ever received milrinone	0	0.22	>.99	Nonsignificant
Ever received propofol	0	53.94	<.001	BVR>3.84 with Riker SAS
Ever received dexmedetomidine	0	61.86	<.001	BVR>3.84 with Riker SAS
Ever received midazolam	0	7.06	.22	Nonsignificant
Ever received ketamine	0	5.74	.33	Nonsignificant
Ever received fentanyl	0	21.16	<.001	BVR>3.84 with Riker SAS
Ever received cisatracurium	0	30.43	<.001	BVR>3.84 with Riker SAS
Ever received insulin infusion	0	54	<.001	BVR>3.84 with glucose
No. of antibiotics[i]	0	53.77	<.001	R^2<0.10
Laboratory results[j]				
White blood cells	8.2	43.18	<.001	R^2<0.10
Hemoglobin	8.1	57.40	<.001	R^2<0.10
BUN	5.5	189.38	<.001	Direct effect: GCS; creatinine; glucose
Creatinine	3.6	191.64	<.001	Direct effect: BUN
Glucose	2.1	69.9	<.001	Direct effect: BUN
Mechanical ventilation				
PEEP[k]	18.5	627.06	<.001	Direct effect: BMI; F_{IO_2}
F_{IO_2}[l]	13.6	220.82	<.001	Direct effect: PEEP
Days to MV initiation[m]	0	51.81	<.001	Direct effect: GCS

Abbreviations: BMI, body mass index; BUN, serum (blood) urea nitrogen; BVR, bivariate residual; CCI, Charlson Comorbidity Index; F_{IO_2}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SAS, Sedation-Agitation Scale.

[a] Nonsignificant indicators, those with R^2 values <0.10, and those with BVR values >3.84 were removed from the model.
[b] Body mass index, calculated as weight in kilograms divided by height in meters squared.
[c] Whether the patient is single or has a significant other.
[d] Patient's living arrangement before hospitalization.
[e] First GCS score after admission.
[f] Mean values in the 24 hours after MV initiation.
[g] Mean score in the 24 hours after MV initiation.
[h] From administrations in first 7 days of ICU admission.
[i] From administrations in 24 hours following MV initiation.
[j] Mean values in within 24 hours of MV initiation.
[k] First PEEP setting of MV episode.
[l] Mean F_{IO_2} in 24 hours after MV initiation.
[m] Days from ICU admission to MV initiation.

Supplemental Table 2
Demographics and baseline characteristics of overall sample (N=934)

Demographic/baseline characteristic	Value[a]
Age, y	60 (48-68)
Sex	
Male	513 (54.9)
Female	421 (45.1)
Race	
White	817 (87.5)
African American/Black	68 (7.3)
Hispanic/Latino of any race	20 (2.1)
Asian	8 (0.9)
American Indian/Alaska Native	8 (0.9)
Native Hawaiian/Pacific Islander	1 (0.1)
Multiracial/2 or more races	6 (0.6)
Unknown/declined to respond	6 (0.6)
Marital status	
No partner	515 (55.1)
Single	296 (31.7)
Divorced	131 (14.0)
Separated	13 (1.4)
Widowed	75 (8.0)
Partner	353 (37.8)
Married	345 (36.9)
Life partner	8 (0.9)
Unknown/unspecified	66 (7.1)
Primary language	
English	915 (98.0)
Spanish	9 (1.0)
Other	10 (1.1)
Insurance status	
Commercial insurance	182 (19.5)
Medicaid	224 (24.0)
Medicare	497 (53.2)
Veterans Affairs/Tricare	18 (1.9)
Other	13 (1.4)
Preadmission living arrangement	
Home	644 (69.0)
With another in home	500 (53.5)
Alone in home	144 (15.4)
Care facility	78 (8.4)
Skilled nursing facility	39 (4.2)
Intermediate care facility	34 (3.6)
Assisted living	5 (0.5)
Community	27 (2.9)
Group home	7 (0.7)
Prison/jail	12 (1.3)
Shelter	2 (0.2)
Homeless	6 (0.6)
Unknown	185 (19.8)

[a] Median (IQR) or number (percentage).

Supplemental Table 3
In-ICU clinical characteristics of overall sample (N=934)

In-ICU clinical characteristic	Value[a]
Charlson Comorbidity Index	
Myocardial infarction	43 (4.6)
Congestive heart failure	129 (13.8)
Peripheral vascular disease	44 (4.7)
Cerebrovascular accident	Excluded
Dementia	9 (1.0)
Chronic pulmonary disease	203 (21.7)
Connective tissue disease	10 (1.1)
Peptic ulcer disease	19 (2.0)
Liver disease	
Mild	46 (4.9)
Moderate to severe	44 (4.7)
Diabetes	
Uncomplicated	134 (14.3)
With end-organ damage	44 (4.7)
Hemiplegia	Excluded
Moderate to severe chronic kidney disease	105 (11.2)
Solid tumor	
Localized	67 (7.2)
Metastatic	22 (2.4)
Leukemia	10 (1.1)
Lymphoma	12 (1.3)
AIDS	5 (0.5)
Charlson Comorbidity Index total score	2 (1-4)
Primary admission diagnosis	
Respiratory	347 (37.2)
Acute	338 (36.2)
Chronic	9 (1.0)
Sepsis	238 (25.5)
Alcohol-related, poisoning, or self-harm	93 (10.0)
Seizures, encephalopathy, or other neurologic alteration	71 (7.6)
Metabolic disorder	51 (5.5)
Heart failure, myocardial ischemia, or arrhythmia	42 (4.5)
Hemorrhage	37 (4.0)
Malignant neoplasm	13 (1.4)
Other	42 (4.5)
Weight, kg	90.0 (71.2-111.0)
BMI[b]	30.5 (24.96-37.7)
Underweight	25 (3.3)
Normal weight	154 (20.1)
Overweight	191 (24.9)
Obesity class I	144 (18.8)
Obesity class II	86 (11.2)
Obesity class III	166 (21.7)
GCS score[c]	7 (4-11)
Vital signs[d]	
Temperature, °C	36.8 (36.3-37.2)
Heart rate, beats per minute	88.8 (76.5-102.3)
Respiratory rate, breaths per minute	21.9 (19.2-25.3)
Blood pressure, mm Hg	
Systolic	105.8 (98.2-113.9)
Diastolic	63.8 (58.9-69.5)
Mean arterial	77.4 (72.2-83.7)
Oxygen saturation, %	95.9 (94.1-97.5)
Riker SAS score[e]	3.0 (2.2-3.4)
Ever coma	263 (28.2)
Laboratory results[f]	
Creatinine, mg/dL	1.2 (0.8-2.2)
Serum urea nitrogen, mg/dL	23 (14-38)
Blood glucose, mg/dL	141 (115-185)
White blood cells, x1000/μL	12.8 (9.1-17.4)
Hemoglobin, g/dL	10.9 (9.0-13.1)
Hematocrit, %	34 (28-40)

Continued

Supplemental Table 3
Continued

In-ICU clinical characteristic	Value[a]
First ventilation mode	
Volume control	645 (69.1)
Pressure support	92 (9.9)
Other	29 (3.1)
Unknown	168 (18.0)
Settings	
PEEP[g] cm H_2O	8 (5-10)
F_{IO_2}[h]	0.46 (0.38-0.59)
Days to MV initiation[i]	0.7 (0.5-0.9)
Continuous infusions[j]	
Vasopressors	
Ever on pressors	364 (39.0)
If yes: number of different types of vasopressors	1 (1-2)
Ever on norepinephrine	357 (38.2)
Ever on vasopressin	76 (8.1)
Ever on epinephrine	70 (7.5)
Ever on phenylephrine	20 (2.1)
Ever on dopamine	3 (0.3)
Inotropes	
Ever on dobutamine	45 (4.8)
Ever on milrinone	4 (0.4)
Sedatives/analgesics/neuromuscular blockers	
Ever on propofol	577 (61.8)
Ever on dexmedetomidine	379 (40.6)
Ever on midazolam	13 (1.4)
Ever on ketamine	9 (1.0)
Ever on fentanyl	653 (69.9)
Ever on cisatracurium	32 (3.4)
Ever on insulin infusion	113 (12.1)
Antimicrobials[k]	
Number of antibiotics	2 (1-3)
Prescribed antifungals	26 (2.8)
Prescribed antivirals	104 (11.1)

Abbreviations: BMI, body mass index; F_{IO_2}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SAS, Sedation-Agitation Scale.

[a] Number (percentage) or median (IQR).
[b] Calculated as weight in kilograms divided by height in meters squared. Percentages are of 766 patients with recorded BMI.
[c] First GCS score after admission.
[d] Mean values in the 24 hours after MV initiation.
[e] Mean score in the 24 hours after MV initiation.
[f] Mean values within 24 hours of MV initiation.
[g] First PEEP setting of MV episode.
[h] Mean F_{IO_2} in 24 hours after MV initiation.
[i] Days from ICU admission to MV initiation.
[j] From administrations in first 7 days of ICU admission.
[k] From administrations in 24 hours following MV initiation.

Supplemental Table 4
Final bivariate residuals in latent class analysis

Indicator	BMI[a]	GCS[b]	Riker SAS[c]	BUN[d]	Creatinine[d]	Glucose[d]	PEEP[e]	F_{IO_2}[f]	Days to MV[g]
BMI[a]	.								
GCS[b]	0.7994	.							
Riker SAS[c]	1.4673	0	.						
BUN[d]	1.885	0	0.6022	.					
Creatinine[d]	1.6398	0.3103	0.7805	0	.				
Glucose[d]	0.9816	1.8698	0.6268	0	1.641	.			
PEEP[e]	0	1.5785	0.4759	1.6202	1.0596	3.0521	.		
F_{IO_2}[f]	2.2934	2.195	1.3366	0.5424	0.3944	0.5017	0	.	
Days to MV[g]	1.128	0	0.2605	0.4114	1.3333	0.6786	0.3943	1.0007	.

Abbreviations: BMI, body mass index; BUN, serum (blood) urea nitrogen; F_{IO_2}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SAS, Sedation-Agitation Scale.

[a] Calculated as weight in kilograms divided by height in meters squared.
[b] First GCS score after admission.
[c] Mean score in the 24 hours after MV initiation.
[d] Mean values within 24 hours of MV initiation.
[e] First PEEP setting of MV episode.
[f] Mean F_{IO_2} in 24 hours after MV initiation.
[g] Days from ICU admission to MV initiation.

Supplemental Table 5
Demographic and clinical characteristics stratified by subgroup (N=934)[a]

Demographic or clinical characteristic	Class 1 (n=367)	Class 2 (n=220)	Class 3 (n=113)	Class 4 (n=105)	Class 5 (n=72)	Class 6 (n=57)	*P*
Age, y	61.0 (49.0-69.0)	58.0 (43.0-69.0)	60.0 (53.5-68.0)	57.0 (44.0-67.0)	63.0 (49.0-69.0)	55.5 (50.0-65.0)	.66
Sex							.42
Male	197 (53.7)	126 (57.3)	53 (46.9)	61 (58.1)	42 (58.3)	34 (59.6)	
Female	170 (46.3)	94 (42.7)	60 (53.1)	44 (41.9)	30 (41.7)	23 (40.4)	
Insurance status							.08
Commercial insurance	61 (16.6)	50 (22.7)	20 (17.7)	19 (18.1)	15 (20.8)	17 (29.8)	
Medicaid	100 (27.2)	59 (26.8)	24 (21.2)	18 (17.1)	18 (25.0)	5 (8.8)	
Medicare	193 (52.6)	106 (48.2)	64 (56.6)	66 (62.9)	35 (48.6)	33 (57.9)	
Other	13 (3.5)	5 (2.3)	5 (4.4)	2 (1.9)	4 (5.6)	2 (3.5)	
CCI total score	3.0 (1.0-4.5)	2.0 (0.0-3.0)	3.0 (1.5-5.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	3.0 (2.0-4.0)	<.001[b]
BMI[c]	27.5 (23.1-32.1)	32.9 (26.9-39.5)	33.5 (25.9-45.7)	40.6 (29.7-46.2)	32.6 (28.5-37.7)	28.6 (22.6-32.9)	<.001[b]
GCS score[d]	7.0 (6.0-10.0)	7.0 (3.0-10.0)	15.0 (14.5-15.0)	11.0 (8.0-14.0)	6.0 (3.0-9.0)	15.0 (14.0-15.0)	<.001[b]
Vital signs[e]							
Temperature, °C	36.7 (36.3-37.2)	36.8 (36.4-37.3)	36.7 (35.9-37.1)	36.8 (36.5-37.4)	36.7 (36.2-37.7)	36.6 (35.9-37.2)	.03[b]
Heart rate, beats per minute	86.3 (74.2-99.5)	89.3 (76.8-103.5)	76.0 (64.3-87.5)	83.5 (74.6-98.7)	92.2 (84.8-101.2)	80.9 (73.0-97.2)	.09
Respiratory rate, breaths per minute	20.0 (17.2-22.6)	22.2 (19.3-26.0)	21.3 (18.9-23.1)	22.2 (19.6-25.1)	23.3 (19.4-25.7)	23.3 (19.4-25.7)	<.001[b]
Blood pressure, MAP, mm Hg	80.3 (74.0-87.6)	77.1 (72.8-83.6)	84.9 (76.1-97.1)	76.3 (70.9-86.0)	74.8 (69.8-80.1)	75.3 (71.2-81.0)	<.001[b]
Oxygen saturation, %	96.7 (95.3-98.1)	95.0 (93.7-96.7)	93.4 (92.8-95.2)	95.6 (94.0-97.2)	96.2 (93.8-98.1)	95.4 (94.3-97.7)	<.001[b]
Riker SAS[f]	3.0 (2.4-3.4)	3.0 (2.2-3.5)	4.0 (4.0-4.0)	3.1 (2.8-3.5)	3.0 (2.3-3.4)	3.0 (2.2-3.3)	<.001[b]
Laboratory results[g]							
White blood cells, x1000/μL	11.2 (8.2-15.0)	13.4 (9.9-17.3)	11.9 (9.5-15.5)	12.3 (8.9-18.7)	14.6 (11.8-18.4)	11.7 (7.2-16.5)	<.001[b]
Hemoglobin, g/dL	10.9 (9.1-12.6)	11.6 (9.8-13.4)	10.1 (8.2-12.6)	9.4 (8.6-11.1)	9.4 (8.4-11.9)	10.1 (8.0-12.1)	<.001[b]
Hematocrit, %	33.5 (28.5-38.0)	36.0 (30.0-41.0)	31 (27.8-37.8)	30.0 (26.0-36.0)	29.0 (26.3-36.5)	30.8 (25.5-35.7)	<.001[b]
BUN, mg/dL	18.2 (12.0-29.7)	20.4 (13.0-28.0)	23 (17.3-37.3)	43.0 (26.0-62.0)	76.5 (53.7-95.5)	13.8 (10.0-17.7)	<.001[b]
Creatinine, mg/dL	0.9 (0.7-1.4)	1.1 (0.8-1.6)	1.1 (0.8-2.0)	2.9 (1.9-4.3)	3.4 (2.4-4.5)	0.8 (0.6-1.4)	<.001[b]
Glucose, mg/dL	122.1 (106.8-160.8)	148.4 (121.0-201.0)	130.5 (113.3-142.8)	136.0 (113.7-154.0)	262.3 (128.3-402.4)	121.5 (97.0-160.5)	<.001[b]
Ventilation settings							
PEEP,[h] cm H_2O	5.0 (5.0-5.0)	10.0 (8.0-11.0)	8.0 (5.0-11.0)	8.0 (5.0-10.0)	8.0 (5.0-10.0)	6.5 (5.0-10.0)	<.001[b]
F_{IO_2}[i]	0.38 (0.33-0.44)	0.51 (0.42-0.65)	0.63 (0.40-0.71)	0.44 (0.40-0.57)	0.49 (0.39-0.54)	0.57 (0.43-0.74)	<.001[b]
Spo_2:F_{IO_2} ratio	260.5 (224.4-300.9)	182.0 (142.7-230.5)	170.6 (129.5-203.4)	218.9 (172.4-257.0)	204.4 (176.2-276.2)	185.8 (141.6-241.5)	<.001
Days to MV initiation[j]	0.7 (0.4-0.7)	0.6 (0.4-0.8)	0.7 (0.6-0.9)	0.7 (0.5-1.0)	0.7 (0.5-0.8)	2.4 (1.5-3.8)	<.001[b]
Continuous infusions[k]							
Vasopressors							
Ever on vasopressors	113 (30.8)	102 (46.4)	18 (15.9)	55 (52.4)	44 (61.1)	32 (56.1)	<.001[l]
Ever on norepinephrine	109 (29.7)	101 (45.9)	17 (15.0)	55 (52.4)	44 (61.1)	31 (54.4)	<.001[m]
Ever on vasopressin	14 (3.8)	27 (12.3)	4 (3.5)	8 (7.6)	15 (20.8)	8 (14.0)	<.001[m]
Ever on epinephrine	16 (4.4)	29 (13.2)	2 (1.8)	5 (4.8)	11 (15.3)	7 (12.3)	<.001[m]
Ever on phenylephrine	5 (1.4)	6 (2.7)	1 (0.9)	4 (3.8)	1 (1.4)	3 (5.3)	.22
Ever on dopamine	2 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	>.99
Sedatives/analgesics							
Ever on propofol	262 (71.4)	178 (80.9)	10 (8.8)	55 (52.4)	48 (66.7)	24 (42.1)	<.001[l]
Ever on dexmedetomidine	156 (42.5)	117 (53.2)	12 (10.6)	40 (38.1)	30 (41.7)	24 (42.1)	<.001[l]
Ever on midazolam	3 (0.8)	4 (1.8)	0 (0.0)	1 (1.0)	2 (2.8)	3 (5.3)	.07
Ever on ketamine	1 (0.3)	3 (1.4)	1 (0.9)	2 (1.9)	1 (1.4)	1 (1.8)	.23
Ever on fentanyl	282 (76.8)	197 (89.5)	14 (12.4)	71 (67.6)	56 (77.8)	33 (57.9)	<.001[l]
Ever on cisatracurium	3 (0.8)	16 (7.3)	2 (1.8)	3 (2.9)	1 (1.4)	7 (12.3)	<.001[m]
Ever on insulin infusion	27 (7.4)	26 (11.8)	9 (8.0)	9 (8.6)	30 (41.7)	12 (21.1)	<.001[l]

Abbreviations: BMI, body mass index; BUN, serum (blood) urea nitrogen; CCI, Charlson Comorbidity Index; F_{IO_2}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; ICU, intensive care unit; MAP, mean arterial pressure; MV, mechanical ventilation; PEEP, positive end-expiratory pressure; SAS, Sedation-Agitation Scale; Spo_2, oxygen saturation as measured by pulse oximetry.

[a] Values are expressed as median (IQR) or number (percentage) of patients.
[b] Difference among 6 groups determined by Kruskal-Wallis test.
[c] Calculated as weight in kilograms divided by height in meters squared.
[d] First GCS score after admission.
[e] Mean values in the 24 hours after MV initiation.
[f] Mean score in the 24 hours after MV initiation.
[g] Mean values within 24 hours of MV initiation.
[h] First PEEP setting of MV episode.
[i] Mean F_{IO_2} in 24 hours after MV initiation.
[j] Days from ICU admission to MV initiation.
[k] From administrations in first 7 days of ICU admission.
[l] Difference among 6 groups determined by χ^2 test of independence.
[m] Difference among 6 groups determined by Fisher exact test.

Supplemental Table 6
Diagnoses by class (N=934)[a]

Primary admission diagnosis[b]	Class 1 (n=367)	Class 2 (n=220)	Class 3 (n=113)	Class 4 (n=105)	Class 5 (n=72)	Class 6 (n=57)
Respiratory	114 (31.1)	91 (41.4)	72 (63.7)	36 (34.3)	21 (29.2)	13 (22.8)
Sepsis	67 (18.3)	71 (32.3)	19 (16.8)	35 (33.3)	31 (43.1)	15 (26.3)
Alcohol-related, poisoning, or self-harm	60 (16.3)	23 (10.5)	1 (0.9)	5 (4.8)	2 (2.8)	2 (3.5)
Seizures, encephalopathy, other neurologic alteration	45 (12.3)	12 (5.5)	1 (0.9)	5 (4.8)	3 (4.2)	5 (8.8)
Other	81 (22.1)	23 (10.5)	20 (17.7)	24 (22.9)	15 (20.8)	22 (38.6)
Metabolic disorder	27 (7.4)	4 (1.8)	1 (0.9)	9 (8.6)	6 (8.3)	4 (7.0)
Heart failure, myocardial ischemia, or arrhythmia	10 (2.7)	5 (2.3)	12 (10.6)	7 (6.7)	4 (5.6)	4 (7.0)
Hemorrhage	22 (6.0)	5 (2.3)	0 (0.0)	4 (3.8)	4 (5.6)	2 (3.5)
Malignant neoplasm	3 (0.8)	3 (1.4)	4 (3.5)	1 (1.0)	0 (0.0)	2 (3.5)
Other	19 (5.2)	6 (2.7)	3 (2.7)	3 (2.9)	1 (1.4)	10 (17.5)

[a] Values are expressed as number (%) of patients. Differences among the 6 groups were determined by χ^2 test of independence.
[b] $P<.001$.