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F_{IO_2} Trajectory as a Pragmatic Intermediate Marker in Acute Hypoxic Respiratory Failure

Sarah J Chalmers, Yewande E Odeyemi, Amos Lal, Heyi Li, Ryan D Frank, Ognjen Gajic, and Hemang Yadav

BACKGROUND: Several markers of oxygenation are used as prognostic markers in acute hypoxemic respiratory failure. Real-world use is limited by the need for invasive measurements and unreliable availability in the electronic health record. A pragmatic, reliable, and accurate marker of acute hypoxemic respiratory failure is needed to facilitate epidemiologic studies, clinical trials, and shared decision-making with patients. F_{IO_2} is easily obtained at the bedside and from the electronic health record. The F_{IO_2} trajectory may be a valuable marker of recovery in patients with acute hypoxemic respiratory failure. METHODS: This was a historical cohort study of adult subjects admitted to an ICU with acute hypoxemic respiratory failure secondary to community-acquired pneumonia and/or ARDS. RESULTS: Our study included 2,670 subjects. F_{IO_2} and S_{pO_2} were consistently more available than was P_{aO_2} in the electronic health record: (F_{IO_2} vs S_{pO_2} vs P_{aO_2} : 100 vs 100 vs 72.8% on day 1, and 100 vs 99 vs 21% on day 5). A worsening F_{IO_2} trajectory was associated with reduced ventilator-free days. From days 2 to 5, every increase in F_{IO_2} by 10% from the previous day was associated with fewer ventilator-free days (on day 2: adjusted mean –1.25 [95% CI –1.45 to –1.05] d, $P < .001$). The S_{pO_2}/F_{IO_2} trajectory also provided prognostic information. On days 3 – 5, an increase in S_{pO_2}/F_{IO_2} from the previous day was associated with increased ventilator-free days (on day 3: adjusted mean 2.09 (95% CI 1.44–2.74) d; $P < .001$). S_{pO_2}/F_{IO_2} models did not add predictive information compared with models with F_{IO_2} alone (on day 2: adjusted F_{IO_2} vs S_{pO_2}/F_{IO_2} R^2 0.122 vs 0.119; and on day 3: 0.153 vs 0.163). CONCLUSIONS: F_{IO_2} and S_{pO_2}/F_{IO_2} are pragmatic and readily available intermediate prognostic markers in acute hypoxic respiratory failure. The F_{IO_2} trajectory in the first 5 d of ICU admission provided important prognostic information (ventilator-free days). Although the S_{pO_2}/F_{IO_2} trajectory was also associated with ventilator-free days, it did not provide more information than the F_{IO_2} trajectory alone. *Key words: acute hypoxic respiratory failure; electronic health record; hypoxia; pneumonia; acute respiratory distress syndrome; prognosis.* [Respir Care 0;0(0):1–●. © 0 Daedalus Enterprises]

Introduction

Acute hypoxic respiratory failure is a common diagnosis that leads to ICU admission.[1,2] In patients with acute hypoxic respiratory failure, the disease course is variable and unpredictable, ranging from rapid improvement or decline to slow improvement or decline, or to persistent disease that becomes chronic.[3] Our ability to objectively identify the changing disease trajectory day to day in clinical practice and for research purposes is limited in part by a lack of an accurate, reliable, and pragmatic intermediate pulmonary physiologic marker. Intermediate markers are biologic measurements, signs, or symptoms that outwardly reflect the underlying disease process.[4-6]

An accurate, reliable, pragmatic pulmonary physiologic marker would improve early identification of the clinical course of patients with acute hypoxic respiratory failure. This will provide clinicians with timely information to guide shared decision-making and assist with evolving patient and family counseling. Intermediate markers can also be used as surrogate end points in clinical trials. Compared with traditional end points, for example, mortality, surrogate end points occur earlier in the disease course and thus clinical trials powered for surrogate end points

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require fewer participants, shorter study duration, and hence cost less.[5,7] In addition, as we continue to embark on the era of "big data," there is a need to identify an intermediate marker for acute hypoxic respiratory failure that can be reliably and accurately extracted from the electronic health record. This marker should be applicable to all patients with acute hypoxic respiratory failure, whether they require mechanical ventilation or another modality of supplemental oxygen delivery.

Several pulmonary physiologic markers have been studied in acute hypoxic respiratory failure.[8] P_{aO_2} and P_{aO_2}/F_{IO_2} are possibly the most widely used measures. It has been shown to correlate with disease severity in patients with acute hypoxic respiratory failure secondary to ARDS and is often used in clinical research to assess treatment response.[9] It is often used in clinical trials to stratify subjects based on disease severity, as an intermediate pulmonary physiologic marker that defines the disease course, or as a surrogate end point, which indicates response to treatment. P_{aO_2}/F_{IO_2} is intended as an intermediate pulmonary physiologic marker of oxygenation but can be unreliable for this purpose. Studies have demonstrated variability in P_{aO_2}/F_{IO_2} with a change in PEEP, F_{IO_2}, oxygen consumption, and other factors.[10-13]

Moreover, intrinsic measurement bias exists: many patients do not undergo arterial blood gas analysis, especially if they are not on mechanical ventilation or are outside of the initial hours of ICU admission. The oxygenation index attempts to resolve some limitations of the P_{aO_2}/F_{IO_2} measurement by incorporating the mean airway pressure but, again, with varying results.[8,14,15] The oxygenation index is also only applicable to patients who are intubated and requires documentation of the mean airway pressure in the electronic health record for pragmatic use. Other physiologic parameters that have been evaluated include the oxygen saturation index, dead space fraction, and lung injury score.[16,17] As with P_{aO_2}/F_{IO_2} and the oxygenation index, the utility of these markers is limited by their requirement for invasive measures, radiation-generating procedures, complex calculations, and unreliable availability in the electronic health record, and/or only apply to a small subpopulation of patients with acute hypoxic respiratory failure.

Oxygen saturation and S_{pO_2}/F_{IO_2} have been shown to correlate with P_{aO_2}/F_{IO_2} in predicting and diagnosing ARDS.[18-22] It has been validated as a replacement marker for P_{aO_2}/F_{IO_2} when determining disease severity in adult and pediatric patients with a critical illness and acute hypoxic respiratory failure.[23-25] Clinical characteristics and outcomes such as mechanical ventilation duration and ICU and hospital length of stay are similar between those diagnosed with ARDS when using S_{pO_2}/F_{IO_2} as opposed to P_{aO_2}/F_{IO_2}.[16] Both S_{pO_2} and F_{IO_2} are easily accessible at the bedside (regardless of the oxygen delivery device) and in the electronic health record. In hospitalized patients treated with supplemental oxygen, S_{pO_2} is relatively constant. The patient care team tightly regulates S_{pO_2} within a narrow range of usually >90%. This is particularly true in the ICU, where S_{PO_2} monitoring is continuous and nursing and respiratory therapy staff support is readily available. Variations within this range of S_{PO_2} would not significantly alter the S_{pO_2}/F_{IO_2}; therefore, the more illustrative variable within S_{pO_2}/F_{IO_2} is F_{IO_2} alone. In this study, we hypothesized that the change in F_{IO_2} (ie, the F_{IO_2} trajectory)

QUICK LOOK

Current knowledge

Although several physiologic markers of oxygenation have been studied, their utility is limited by cost, the risk related to invasive technique or radiation, complex calculations, and/or a lack of accessibility, particularly from the electronic heath record. P_{aO_2}/F_{IO_2} is one example of a commonly used marker used clinically to monitor the disease course; however, it has not been validated for this purpose and is unreliable as a prognostic marker in patients with higher needs.

What this paper contributes to our knowledge

The F_{IO_2} trajectory (the change in F_{IO_2} concentration from the previous day) was easily accessible at the bedside and from the electronic health record. In addition, on days 2 – 5, it was associated with the patient outcome of ventilator-free days and can be used as an early (or intermediate) marker to predict patient outcomes.

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alone is associated with the clinically relevant patient outcome of ventilator-free days. We also hypothesized that the F_{IO_2} trajectory would be at least as reliable as S_{pO_2}/F_{IO_2} as an intermediate physiologic marker in acute hypoxic respiratory failure.

Methods

Design, Subjects, and Definitions

We performed a historical cohort study by using a convenience sample of 2,771 adult subjects (>18 y old) admitted to the Mayo Clinic–Rochester ICU with community-acquired pneumonia and/or ARDS between January 1, 2009, and June 30, 2014. Development of this cohort was previously described.[26] We included all patients with acute hypoxic respiratory failure. Acute hypoxic respiratory failure was defined as requiring supplemental oxygen by any modality at any point within the first 5 d after ICU admission. Community-acquired pneumonia was defined as per the 2007 Infectious Disease Society of America/American Thoracic Society guidelines[27] on community acquired pneumonia and identified by the *International Classification of Disease, Ninth Edition* codes 481–486. ARDS was defined by the 2012 Berlin criteria[9] and identified through manual chart review by two independent reviewers. The Mayo Clinic Institutional Review Board reviewed and approved this study, and a waiver of consent was granted. Per Mayo Clinic policy, subjects who had previously declined the use of their medical record data were excluded from this study.

Data Collection

Data were collected by using the METRIC Data Mart System which is an electronic health record based data warehouse with near real-time data input. The development, structure, and data collection methods of this system were previous described.[28] The automated system was supplemented by manual review as needed. Data were collected from the first patient admission. Subsequent admissions were omitted. We collected baseline data, which included demographics, comorbid conditions (Charlson comorbidity index), admission diagnoses, illness severity as measured by APACHE (Acute Physiology and Chronic Health Evaluation) III and Sequential Organ Failure Assessment (SOFA) score, and the respiratory failure severity as measured by respiratory SOFA. For those subjects who met the inclusion criteria, all available measures of F_{IO_2}, S_{pO_2}, and P_{aO_2} available within the 5-d measurement period were collected. Oxygen delivery devices (nasal cannula, simple face mask, and high flow nasal cannula) were documented in the electronic health record in L/min. The widely accepted conversion of 4% F_{IO_2} per liter of flow was used to convert from L/min to percent F_{IO_2}.[18,29]

Statistical Analysis

Data were summarized by using counts and percentages for categorical variables, and medians (interquartile ranges) for continuous variables. Differences across F_{IO_2} levels at ICU admission, were categorized into tertiles of <0.35, 0.35–0.49, 0.50 and were compared by using chi-square tests for categorical variables (sex, race, ethnicity, presence of community-acquired pneumonia, ARDS, COPD, asthma, respiratory SOFA, invasive ventilator and noninvasive ventilator use, hospital mortality, 30-d mortality, and 1-year mortality) and the Kruskal-Wallis test for continuous variables (age, APACHE III, SOFA, invasive ventilator days, noninvasive ventilator days, hospital length of stay, and ICU length of stay).

The primary outcome for this study was ventilator-free days. Ventilator-free days were defined as the number of days that the subject was alive and not requiring invasive mechanical ventilation within 28 d of the study day. Associations between the daily F_{IO_2} measures and ventilator-free days were analyzed on ICU day 1 through day 5 by using linear regression models. For day 1, the F_{IO_2} value was the average over the first 6 h of day 1 of the ICU admission. For subsequent days, the 6-h average of the last proceeding day was used. For example, on day 2, the average F_{IO_2} from hours 18 to 24 were used. For each model, we performed unadjusted univariate analyses as well as adjusted for the a priori clinically relevant adjustment variables of age, sex, Charlson comorbidity index, respiratory SOFA, and day 1 F_{IO_2} (for days 2 – 5). For days 2 through 5, we analyzed the association of F_{IO_2} on the current day and from the previous day with ventilator-free days. The same adjustment terms were used for these models. These analyses were repeated by using daily values of S_{pO_2}/F_{IO_2} for comparative purposes. The adjusted R^2 was reported for each linear regression model to compare the performance of models with F_{IO_2} measures alone to measures with S_{pO_2}/F_{IO_2}. All analyses were performed in SAS version 9.4 (SAS Institute, Cary, North Carolina). Because we examined daily F_{IO_2} on 5 separate days, we used a Bonferroni correction to account for multiple comparisons. A 2-sided $P < .01$ was considered statistically significant.

Results

A total of 2,670 subjects met our inclusion criteria. One hundred one patients were excluded due to lack of supplemental oxygen requirement. Subject demographics are presented in Table 1 and are categorized by baseline (day 1) F_{IO_2}. The subjects in the 0.35–0.49 or >0.50 category of baseline F_{IO_2} requirement tended to be younger, have

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Table 1. Baseline Demographics and Clinical Characteristics by Categorized Day 1 F_{IO_2}

Characteristic	F_{IO_2} <0.35 (n = 776)	F_{IO_2} 0.35 – 0.49 (n = 985)	F_{IO_2} ≥0.50 (n = 909)	Total (N = 2,670)	P
Demographics					
Age, y	73 (60–82)	72 (59–82)	67 (55–78)	70 (58–81)	.001*
Men	425 (54.8)	551 (55.9)	508 (55.9)	1,484 (55.6)	.86†
Race					.38†
White	729 (93.9)	915 (92.9)	846 (93.1)	2,490(93.3)	
Black	11 (1.4)	13 (1.3)	10 (1.1)	34 (1.3)	
Asian	8 (1.0)	12 (1.2)	6 (0.7)	26 (1.0)	
Other	14 (1.8)	32 (3.2)	25 (2.8)	71 (2.7)	
Unknown	14 (1.8)	13 (1.3)	22 (2.4)	49 (1.8)	
Ethnicity					.33†
Missing, n	34	53	64	151	
Non-Hispanic/Latino	734 (98.9)	917 (98.4)	828 (98.0)	2,479 (98.4)	
Hispanic/Latino	8 (1.1)	15 (1.6)	17 (2.0)	40 (1.6)	
Hospital diagnosis					
Pneumonia	770 (99.2)	977 (99.2)	865 (95.2)	2,612 (97.8)	.001†
ARDS	6 (0.8)	8 (0.8)	44 (4.8)	58 (2.2)	.001†
Comorbidities					
Charlson comorbidity index	7 (4–10)	7 (4–9)	6 (3–9)	6 (4–9)	.001*
COPD	232 (29.9)	282 (28.6)	181 (19.9)	695 (26.0)	.001†
Asthma	103 (13.3)	130 (13.2)	83 (9.1)	316 (11.8)	.008†
Illness severity					
APACHE III score	65 (54–78)	72 (58–87)	78 (61–95)	71 (57–87)	.001*
SOFA	4 (2–6)	6 (4–8)	6 (4–9)	5 (3–8)	.001*
Respiratory SOFA score					.001†
0	32 (4.1)	26 (2.6)	9 (1.0)	67 (2.5)	
1	58 (7.5)	83 (8.4)	34 (3.7)	175 (6.6)	
2	652 (84.0)	663 (67.3)	415 (45.7)	1,730 (64.8)	
3	7 (0.9)	129 (13.1)	226 (24.9)	362 (13.6)	
4	27 (3.5)	84 (8.5)	225 (24.8)	336 (12.6)	
Mode of respiratory support					
Invasive ventilator use	290 (37.4)	726 (73.7)	717 (78.9)	1,733 (64.9)	.001†
Invasive ventilator days (n = 1,733)	1.0 (0.3–2.8)	1.3 (0.4–3.2)	3.0 (1.0–6.5)	1.7 (0.6–4.6)	.001*
Noninvasive ventilator use	204 (26.3)	478 (48.5)	388 (42.7)	1,070 (40.1)	.001†
Noninvasive ventilator days (n = 1,070)	0.7 (0.2–1.5)	0.6 (0.2–1.4)	0.7 (0.2–1.9)	0.6 (0.2–1.6)	.21*
Outcomes					
Invasive ventilator-free days	28.0 (25.9–28.0)	26.9 (21.6–27.9)	24.0 (8.1–27.6)	26.9 (19.5–28.0)	.001*
Hospital mortality	316 (4.7)	429 (43.6)	539 (59.3)	1,284 (48.1)	.001†
30-d mortality	336 (43.3)	434 (44.1)	498 (54.8)	1,268 (47.5)	.001†
1-y mortality	544 (70.1)	650 (66.0)	680 (74.8)	1,874 (7.2)	.001†
Hospital LOS, d	6.2 (3.8, 1.4)	7.0 (4.4, 12.0)	8.5 (4.9, 15.5)	7.2 (4.3, 12.6)	.001*
ICU LOS, d	1.2 (.8, 3.2)	2.2 (1.1, 4.5)	3.8 (1.8, 8.0)	2.2 (1.1, 5.2)	.001*

Data are n (%) unless otherwise noted.
* Kruskal-Wallis test.
†Chi-square test.
APACHE = Acute Physiology and Chronic Health Evaluation
SOFA = Sequential Organ Failure Assessment
LOS = length of stay

higher incidence of ARDS, and a lower incidence of community-acquired pneumonia, lower Charlson comorbidity index score, lower presence of COPD and asthma, and higher SOFA, APACHE III, and respiratory SOFA scores. Compared with the subjects in the <35% baseline F_{IO_2} category, a higher percentage of the subjects in the 0.35-0.49 and >0.50 categories required invasive ventilation (37.4, 73.7, and 78.9%, respectively; P = .001) and noninvasive ventilation (26.3, 48.5, and 42.7%, respectively; P = .001) during their ICU stay. The subjects in the 0.35-0.49

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and >0.50 baseline F_{IO_2} categories also had worse clinical outcomes, including fewer ventilator-free days (28.0 vs 26.9 and 24 d; $P = .001$); higher hospital (40.7% vs 43.6% and 59.3%; $P = .001$), 30-day (43.3% vs 44.1% and 54.8%; $P = .001$), and 1-year mortality (70.1% vs 66.0% and 74.8%, $P = .001$); and longer hospital (6.2 vs 7.0 and 8.5 d, $P = .001$) and ICU (1.2 vs 2.2 and 3.8 d, $P = .001$) stays.

The daily percentages of the subject population by F_{IO_2} category on day 1 – 5 are displayed in Figure 1. The percentage of the subjects in the high and mild-moderate F_{IO_2} requirement categories decreased on each consecutive day. On day 1, 34.1% of the subjects had a high F_{IO_2} requirement and 65.1% had a mild-moderate F_{IO_2} requirement. On day 5, 13.2% of the subjects had a high F_{IO_2} requirement and 24.3% had a mild-moderate F_{IO_2} requirement. Conversely, the percentage of the subjects on room air increased exponentially from day 1 to 5, with 0.8% on day 1 and 62.5% on day 5. The mean daily value and the number of subjects with available data for the variables of interest (F_{IO_2}, S_{pO_2}, P_{aO_2}, and S_{pO_2}/F_{IO_2}) are presented in Table 2. The mean F_{IO_2} decreased and the mean S_{pO_2}/F_{IO_2} increased from day 1 to 5, whereas the mean P_{aO_2} and S_{pO_2} remained unchanged. In addition, the number of subjects with available F_{IO_2} and S_{pO_2} was considerably higher compared with those with P_{aO_2}, particularly later in the illness course.

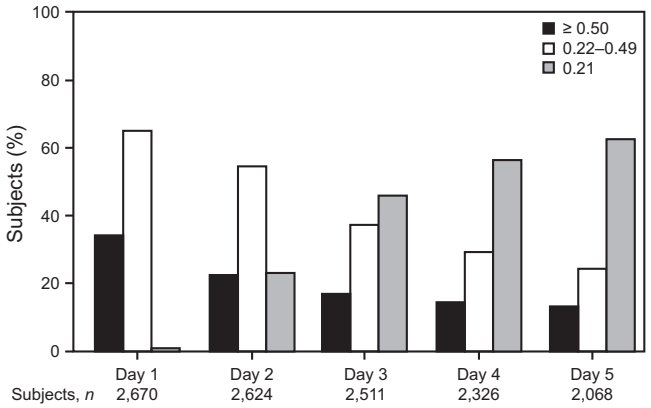

Fig. 1. Percentage of subjects within each F_{IO_2} category on days 1 – 5.

The association between the change in daily F_{IO_2} and S_{PO_2}/F_{IO_2} and ventilator-free days are shown in Tables 3 and 4. In Table 3, the unadjusted increase in F_{IO_2} on days 2 – 5 compared with the previous day showed a significant decrease in ventilator-free days: on day 2: –1.25 (–1.45 to –1.05) d, $P = .001$; on day 3: –1.39 (–1.61 to –1.17) d, $P = .001$; on day 4: –1.55 (–1.81 to –1.28) d, $P = .001$; on day 5: –1.77 (–2.08 to –1.47) d, $P = .001$ for each 10% increase in F_{IO_2} from the previous day. When adjusted for the confounding variables of age, the Charlson comorbidity index, and respiratory SOFA but not of sex, the association remained significant. Similar results were seen when analyzed by the F_{IO_2} category, as depicted in Figure 2. In Table 4, the unadjusted increase in S_{pO_2}/F_{IO_2} on days 3 – 5 compared with the previous day showed a significant increase in ventilator-free days: on day 3: 2.09 (1.44–2.74) d, $P = .001$; on day 4: 1.38 (0.61–2.16) d, $P = .001$; on day 5: 1.46 (0.56–2.36) d, $P = .001$ for each 100-point increase from the previous day. The association between ventilator-free days and the change in S_{pO_2} / F_{IO_2} on day 2 compared with day 1 was not significant (on day 2: 0.10 (–0.27 to –0.47) d, $P = .60$). Again, when adjusted for the confounding variables, the findings on days 3–5 remained significant. As seen in Supplementary Table 1 (see the supplementary materials at http://www.rcjournal.com), the increasing baseline F_{IO_2} concentration was also associated with significantly fewer ventilator-free days with unadjusted increase, for each 10% increase in F_{IO_2}, of –1.06 (–1.23 to 0.88) d, $P = .001$. The predicted change in ventilator-free day for each 10% change in F_{IO_2} compared with the subjects on >50% on the day of interest and the day before are illustrated in Supplementary Tables 2–5 (see the supplementary materials at http://www.rcjournal.com).

Table 2. F_{IO_2}, S_{pO_2}, and P_{aO_2} Values by Day

Characteristic	Day 1 ($n = 2,670$)	Day 2 ($n = 2,624$)	Day 3 ($n = 2,511$)	Day 4 ($n = 2,326$)	Day 5 ($n = 2,068$)
F_{IO_2}					
n (%)	2,670 (100)	2,624 (100)	2,511 (100)	2,326 (100)	2,068 (100)
Mean ± SD	46.3 ± 16.5	39.8 ± 18.3	34.7 ± 18.1	32.2 ± 17.1	3.8 ± 16.4
S_{PO_2}					
n (%)	2,670 (100)	2,623 (99.9)	2,510 (99.9)	2,325 (99.9)	2,067 (99.9)
Mean ± SD	94.9 ± 2.3	94.7 ± 2.4	94.6 ± 2.6	94.6 ± 2.6	94.5 ± 2.9
P_{aO_2}					
n (%)	1,946 (72.8)	992 (37.8)	719 (28.6)	533 (22.9)	435 (21.0)
Mean ± SD	96.3 ± 34.9	93.5 ± 28.6	92.9 ± 29.6	91.2 ± 28.0	92.8 ± 47.7

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Table 3. Multivariable Associations Between Daily F_{IO_2} Measures and Invasive Ventilator-Free Days by Using Unadjusted and Adjusted Linear Regression Models

Characteristic	*n*	Adjusted Mean (95% CI)*	Adjusted *P**	Adjusted R^2
Day 2				0.122
Day 2 F_{IO_2}, per 0.10	2,624	–1.25 (–1.45 to –1.05)	.001	
Day 1 F_{IO_2}, per 0.10	2,624	–0.30 (–0.49 to –0.10)	.003	
Age, per 10 y	2,624	–0.28 (–0.53 to –0.04)	.03	
Sex			.91	
Women	1,168	0.00 (ref.)		
Men	1,456	–0.04 (–0.70 to 0.63)		
Charlson comorbidity index, per 1 unit	2,624	–0.22 (–0.33 to –0.12)	.001	
Respiratory SOFA, per 1 unit	2,624	–1.47 (–1.89 to –1.05)	.001	
Day 3				0.153
Day 3 F_{IO_2}, per 0.10	2,511	–1.39 (–1.61 to –1.17)	.001	
Day 2 F_{IO_2}, per 0.10	2,511	–0.46 (–0.68 to–0.24)	.001	
Age, per 10 y	2,511	–0.36 (–0.61 to –0.11)	.004	
Sex			.68	
Women	1,128	0.00 (ref)		
Men	1,383	–0.14 (–0.80 to 0.52)		
Charlson comorbidity index, per 1 unit	2,511	–0.20 (–0.30 to –0.10)	.001	
Respiratory SOFA, per 1 unit	2,511	–1.29 (–1.69 to –0.89)	.001	
Day 4				0.168
Day 4 F_{IO_2}, per 0.10	2,326	–1.55 (–1.81 to –1.28)	.001	
Day 3 F_{IO_2}, per 0.10	2,326	–0.46 (–0.71 to –0.20)	.001	
Age, per 10 y	2,326	–0.37 (–0.62 to –0.11)	.005	
Sex			.13	
Women	1,036	0.00 (ref.)		
Men	1,290	–0.52 (–1.20 to 0.15)		
Charlson comorbidity index, per 1 unit	2,326	–0.23 (–0.33 to –0.13)	.001	
Respiratory SOFA, per 1 unit	2,326	–0.99 (–1.39 to –0.58)	.001	
Day 5				0.173
Day 5 F_{IO_2}, per 0.10	2,068	–1.77 (–2.08 to –1.47)	.001	
Day 4 F_{IO_2}, per 0.10	2,068	–0.40 (–0.69 to –0.12)	.006	
Age, per 10 y	2,068	–0.31 (–0.58 to –0.04)	.03	
Sex			.28	
Women	938	0.00 (ref.)		
Men	1,130	–0.40 (–1.13 to 0.32)		
Charlson comorbidity index, per 1 unit	2,068	–0.26 (–0.37 to –0.15)	.001	
Respiratory SOFA, per 1 unit	2,068	–0.65 (–1.08 to –0.22)	.003	

* Mean estimates and *P* values are adjusted for all variables listed within the table.
Ref = reference
SOFA = Sequential Organ Failure Assessment

As a sensitivity analysis, we evaluated the association among F_{IO_2}, S_{pO_2}/F_{IO_2}, and ventilator-free days only in those subjects who required invasive mechanical ventilation. A similar association was seen: F_{IO_2} trajectory: –1.89 (–2.24 to –1.54) d, $P = .001$ on day 2; –1.16 (–1.54 to –0.78) d, $P = .001$ on day 3; –1.79 (–2.29 to –1.30) d, $P = .001$ on day 4; and –1.81 (–2.34 to –1.28) d, $P = .001$ on day 5; and S_{pO_2}/F_{IO_2}: 2.71 (1.11 to 4.31) d, $P = .001$ on day 2; 1.46 (0.21-2.71) d, $P = .02$ on day 3; 0.59 (–1.11 to 2.29) d, $P = 0.49$ on day 4; and 0.32 (–1.54 to 2.18) d, $P = .74$ on day 5 (Supplementary Tables 6 and 7 [see the supplementary materials at http://www.rcjournal.com]).

Discussion

Our results showed that the F_{IO_2} trajectory was associated with ventilator-free days and performed as well as S_{pO_2}/F_{IO_2} as a prognostic marker. Although S_{pO_2}/F_{IO_2} was previously evaluated as a marker of oxygenation, to our knowledge, our study was the first to assess F_{IO_2} trajectory alone.[30,31] Our study also demonstrated the following key findings: (1) F_{IO_2} was more readily available than P_{aO_2}; (2) a higher baseline F_{IO_2} was associated with increased illness severity and worse outcomes; (3) F_{IO_2} was the illustrative variable within the S_{pO_2}/F_{IO_2}, and the F_{IO_2} trajectory

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Table 4. Multivariable Associations Between Daily Changes in S_{pO_2} / F_{IO_2} and Invasive Ventilator-Free Days by Using Unadjusted and Adjusted Linear Regression Models

Characteristic	Adjusted Mean (95% CI)*	Adjusted *P**	Adjusted R^2*
Day 2			0.119
Day 2 F_{IO_2}, per 0.10	–1.30 (–1.54 to –1.06)	.001	
Day 2 S_{pO_2} / F_{IO_2}, per 100	0.10 (–0.27 to 0.47)	.60	
Day 1 S_{pO_2} / F_{IO_2}, per 100	0.01 (–0.34 to 0.35)	.96	
Age, per 10 y	–0.28 (–0.53 to –0.03)	.03	
Sex		.98	
Women	0.00 (ref.)		
Men	–0.01 (–0.68 to 0.66)		
Charlson comorbidity index, per 1 unit	–0.22 (–0.32 to –0.12)	.001	
Respiratory SOFA, per 1 unit	–1.65 (–2.05 to –1.24)	.001	
Day 3			0.163
Day 3 F_{IO_2}, per 0.10	–0.38 (–0.80 to 0.04)	.08	
Day 3 S_{pO_2}/F_{IO_2}, per 100	2.09 (1.44-2.74)	.001	
Day 2 S_{pO_2}/F_{IO_2}, per 100	0.13 (–0.03 to 0.29)	.10	
Age, per 10 y	–.037 (–0.62 to –0.13)	.003	
Sex		.45	
Women	0.00 (ref.)		
Men	–0.25 (–0.91 to 0.40)		
Charlson comorbidity index, per 1 unit	–0.21 (–0.31 to –0.11)	.001	
Respiratory SOFA, per 1 unit	–1.08 (–1.48 to –0.68)	.001	
Day 4			0.178
Day 4 F_{IO_2}, per 0.10	–0.74 (–1.21 to –0.27)	.002	
Day 4 S_{pO_2}/F_{IO_2}, per 100	1.38 (0.61-2.16)	.001	
Day 3 S_{pO_2}/F_{IO_2}, per 100	0.67 (0.26-1.08)	.001	
Age, per 10 y	–0.39 (–0.64 to –0.13)	.003	
Sex		.10	
Women	0.00 (ref.)		
Men	–0.57 (–1.24 to 0.11)		
Charlson comorbidity index, per 1 unit	–0.24 (–0.34 to –0.14)	.001	
Respiratory SOFA, per 1 unit	–0.74 (–1.15 to –0.33)	.001	
Day 5			0.180
Day 5 F_{IO_2}, per 0.10	–0.99 (–1.53 to –0.45)	.001	
Day 5 S_{pO_2} / F_{IO_2}, per 100	1.46 (0.56-2.36)	.001	
Day 4 S_{pO_2} / F_{IO_2}, per 100	0.39 (–0.08 to 0.86)	.11	
Age, per 10 y	–0.33 (–0.61 to –0.06)	.02	
Sex		.26	
Women	0.00 (ref.)		
Men	–0.42 (–1.14 to 0.30)		
Charlson comorbidity index, per 1 unit	–0.27 (–0.38 to –0.16)	.001	
Respiratory SOFA, per 1 unit	–0.45 (–0.89 to –0.02)	.04	

* Mean estimate and *P* value are adjusted for all variables listed within the table.
ref. = reference
SOFA = Sequential Organ Failure Assessment

correlated with the disease course. Unlike other pulmonary physiologic markers, the F_{IO_2} trajectory is readily determined at the bedside and through the electronic health record, and can be used to facilitate pragmatic clinical trials in subjects with acute hypoxic respiratory failure.

Results from our study showed that, in a population of subjects with acute hypoxic respiratory failure secondary to community-acquired pneumonia or ARDS, higher baseline F_{IO_2} alone was associated with increased severity of illness and worse outcomes, including increased invasive and noninvasive ventilator use, mortality, hospital and ICU length of stay, and fewer ventilator-free days. This was consistent with a previous study, which demonstrated that baseline F_{IO_2} is an independent predictor of mortality.[32] Our results showed that daily mean F_{IO_2} concentration decreased and S_{pO_2}/F_{IO_2} increased over time, whereas the daily mean S_{pO_2}

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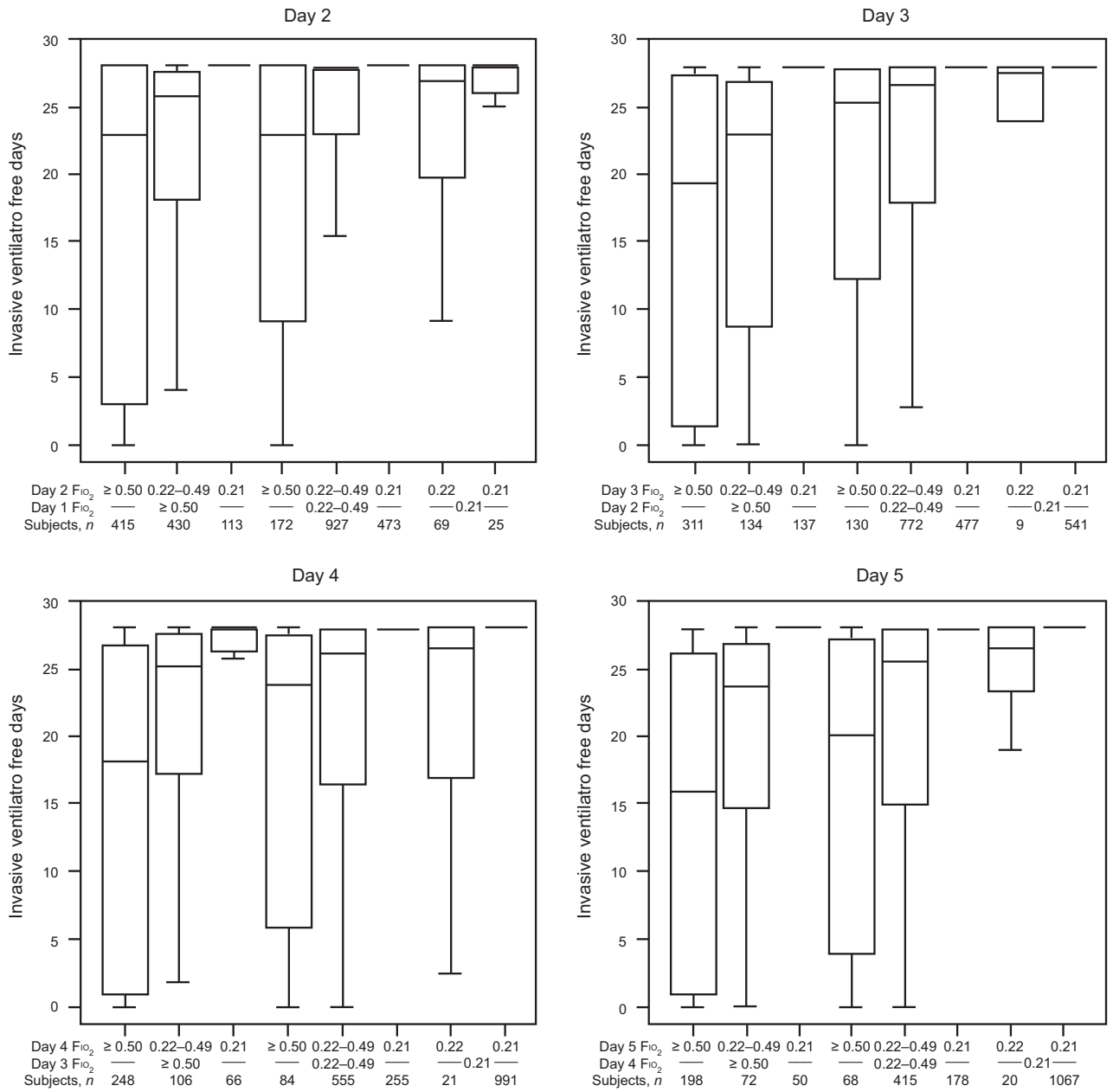

Fig. 2. Association between the change in the F_{IO_2} category compared with the previous day and ventilator-free days.

and P_{aO_2} remained largely unchanged. This highlighted F_{IO_2} as the illustrative variable, which changed over the course of the disease as opposed to S_{PO_2} and P_{aO_2}, which remained relatively constant. The more novel result from our study was the association of the F_{IO_2} trajectory with the patient important outcome of ventilator-free days. In our study, an increase in the F_{IO_2} concentration by $\geq 10\%$ from the previous day was significantly associated with fewer ventilator-free days. S_{pO_2}/F_{IO_2} demonstrated a similar trend in that an increase in S_{pO_2}/F_{IO_2} was associated with more ventilator-free days. Interestingly, the R^2 value, which depicts the strength of the prognostic relationship between the change in F_{IO_2} and the change in S_{pO_2}/F_{IO_2} were similar, which indicated that the addition of S_{pO_2} did not provide a substantial benefit.

Our study identified the F_{IO_2} trajectory as a reliable and pragmatic marker, easily and reliably obtainable at the bedside and from the electronic health record, and associated with the patient important outcome, ventilator-free days. The strengths of our study included the novel assessment of a pragmatic marker, the F_{IO_2} trajectory, the large cohort size, and the broad applicability to patients with acute

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hypoxic respiratory failure due to community-acquired pneumonia and/or ARDS. Our study had limitations. The single-center nature of the study limited overall generalizability, and these findings should be investigated further in a multi-center setting. Determining the F_{IO_2} trajectory also required that bedside teams (nursing, physicians, and respiratory therapists) reduced F_{IO_2} to the minimum required to meet S_{pO_2} and/or P_{aO_2} goals. A potential limitation in doing this study retrospectively was that we were not able to determine this.

However, during the period of our study, all medical ICU subjects followed a respiratory therapy-driven automated protocol (introduced in 2008) to regularly wean supplemental oxygen to the minimum required at multiple times during the day. As such, we can be reasonably confident that the F_{IO_2} administered at any one time had been appropriately titrated. Any future prospective validation of these study findings should include, for example, automated F_{IO_2} titration protocol. Also, in the subjects who were not receiving precise F_{IO_2} (mechanical ventilation, BPAP, CPAP, Venturi device), we used a conversion table to approximate F_{IO_2}. To our knowledge, a validated conversion does not exist, and this method has been used for similar purposes in several previous studies.[18,29] Although this introduced imprecision, it was also a pragmatic necessity because we sought to determine an intermediate marker that can be readily used in a variety of clinical and research settings. Moreover, in our sensitivity analysis of the subjects on invasive mechanical ventilation (in which the exact F_{IO_2} is known), the association between the F_{IO_2} trajectory and ventilator-free days was unchanged (Supplementary Tables 6 and 7 [see the supplementary materials at http://www.rcjournal.com]).

Conclusions

In the subjects who were critically ill and with acute hypoxic respiratory failure secondary to community-acquired pneumonia or ARDS, F_{IO_2} and S_{pO_2} were readily available in the electronic health record, substantially more so than P_{aO_2}. A higher baseline and increase in F_{IO_2} compared with the previous day was associated with fewer ventilator-free days. The F_{IO_2} trajectory was at least as reliable as the S_{pO_2} / F_{IO_2} trajectory and, therefore, the F_{IO_2} trajectory alone may be sufficient to predict patient important outcomes.

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