Symptoms, Pulmonary Function, and Functional Capacity Four Months after COVID-19

To the Editor:

Emerging reports demonstrate persistent symptoms and lung function impairment in survivors of coronavirus disease (COVID-19) discharged from the hospital (1–6). However, little is known about the longer-term impact of COVID-19 in patients not requiring hospitalization. We hypothesized that both hospitalized and nonhospitalized survivors of COVID-19 will have persistent symptoms, impaired pulmonary function, and a diminished functional capacity 3 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

Methods

Patients were prospectively screened and recruited from The Ottawa Hospital administrative registry and from our study website (https://omc.ohri.ca/left/) in sequential order. Patients had to be ⩾18 years of age and diagnosed with SARS-CoV-2 infection by reverse transcriptase–polymerase chain reaction 3 months (+6 wk) before enrollment. The study was approved by The Ottawa Health Science Network Research Ethics Board.

Patients retrospectively reported the presence and severity of symptoms during the acute phase of illness (5-point scale: 0, absent; 4, very severe) and at the 3-month study visit (6-point scale: 0, absent; 5, much worse now). Patients underwent transthoracic echocardiography, pulmonary function testing, and a symptom-limited incremental (15 watts per minute) cycle cardiopulmonary exercise test (7).

Pulmonary function (8, 9) and cycle cardiopulmonary exercise test variables (10) were referenced to predicted normal values. Chronotropic insufficiency (CI) was defined as a heart rate reserve of <0.8 (11).

Mean differences between hospitalized and nonhospitalized patients were evaluated using Student's *t* tests or Mann-Whitney *U* tests. Binary variables were evaluated using a chi-square test. Analyses were performed using SPSS version 9.0 (SAS Institute, Inc.). Statistical significance was set at $P < 0.05$, and values are reported as mean ± standard deviation unless otherwise stated.

Results

Between June and October 2020, 91 patients were screened for eligibility at The Ottawa Hospital. Of these, 15 refused participation and 13 did not meet the inclusion criteria. At the end, 25 hospitalized and 38 nonhospitalized patients were enrolled. The time to follow up was 119.9 ± 16.2 days after the first positive SARS-CoV-2 test result for hospitalized patients and 129.8 ± 16.5 days for nonhospitalized patients. Hospitalized patients were older and had a higher prevalence of comorbid conditions (Table 1).

In both groups, fatigue (hospitalized, 92.0%; nonhospitalized, 97.4%) and exertional breathlessness (hospitalized, 76.0%; nonhospitalized, 81.6%) were frequently reported during the acute phase of COVID-19. At follow up, fatigue (hospitalized, 72.0%; nonhospitalized, 71.1%) and exertional breathlessness (hospitalized, 68.0%; nonhospitalized, 55.3%) persisted as two of the most frequently reported symptoms (Table 1).

Forced vital capacity, total lung capacity (TLC), and the diffusing lung capacity for carbon monoxide (D_{LCO}) were lower in hospitalized patients. Subnormal TLC and D_{LCO} were more prevalent in hospitalized patients. Left ventricular ejection fraction was similar between groups (Table 2).

Peak oxygen consumption ($\dot{V}O_2$) % predicted was lower in hospitalized versus nonhospitalized patients (hospitalized, 64.3 ± 19.2%; nonhospitalized, 83.5 ± 17.9%). Indices of respiratory mechanics, including inspiratory capacity and inspiratory reserve volume, were lower for a given $\dot{V}O_2$ in hospitalized patients (Table 2, Figure 1). Peak heart rate, heart rate reserve, and oxygen pulse were lower, and the ventilatory equivalent for carbon dioxide nadir was higher in hospitalized patients. CI was identified in 68.0% of hospitalized and 18.4% of nonhospitalized patients (Table 2). CI could not be explained by medication use alone, as only 35.0% and 0.0% of hospitalized and nonhospitalized patients with CI, respectively, were receiving heart rate–modifying treatment. Breathlessness and leg discomfort ratings were higher for a given $\dot{V}O_2$ in hospitalized patients but were not different between groups at end-exercise (Table 2, Figure 1). Leg discomfort was the most frequently reported locus of symptom limitation to exercise in both groups, although it occurred at a lower peak $\dot{V}O_2$ in hospitalized versus nonhospitalized patients (Table 2).

Discussion

Consistent with previous studies, we found that hospitalized and nonhospitalized survivors of COVID-19 report persistent fatigue and exertional breathlessness and exhibit impaired lung function and diminished functional capacity 3–4 months after SARS-CoV-2 infection (1–6). Although cardiopulmonary abnormalities were observed in both groups, they were more prevalent and severe in hospitalized patients.

Nonresolving lung parenchymal or pulmonary vascular lesions from the time of the acute infection (4) may account for the higher rate and severity of pulmonary sequelae in

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Table 1. Demographics, baseline characteristics, admission details, and symptoms in hospitalized and nonhospitalized patients with COVID-19

	Hospitalized (*n* = 25)	Nonhospitalized (*n* = 38)
Age, y	59.1 ± 13.5	42.4 ± 12.9
Sex (male, %)	64.0	52.6
BMI, kg/m^2	30.07 ± 7.50	28.17 ± 5.62
Black, Asian, and minority ethnic groups	9 (36)	7 (18.4)
Cigarette smoking		
Never-smoker	17 (68.0)	28 (73.7)
Active smoker	0	0
Past smoker	8 (32.0)	10 (26.3)
Charlson comorbidity index	2.12 ± 1.72	0.37 ± 0.59
Comorbidities		
Obesity (BMI ⩾ 30)	8 (32.0)	13 (34.2)
Hypertension	10 (40.0)	4 (10.5)
Dyslipidemia	10 (40.0)	2 (5.3)
Diabetes	10 (40.0)	1 (2.6)
Asthma (self-reported)	9 (36.0)	9 (23.7)
Chronic obstructive pulmonary disease	0	1 (2.6)
Pulmonary fibrosis	1 (4.0)	0
Obstructive sleep apnea	5 (20.0)	0
Heart failure	1 (4.0)	1 (2.6)
Atrial fibrillation	3 (12.0)	3 (7.9)
Active cancer	5 (20.0)	0
COVID-19 illness		
Symptom prevalence		
Exertional breathlessness	19 (76.0)	31 (81.6)
Mild to moderate	4 (16.0)	22 (57.9)
Severe to very severe	15 (60.0)	9 (23.7)
Fatigue	23 (92.0)	37 (97.4)
Mild to moderate	7 (28.0)	13 (34.2)
Severe to very severe	16 (64.0)	24 (63.2)
Length of hospital stay, d	17.12 ± 17.20	—
Required ICU admission	10 (40.0)	—
Required oxygen	21 (84.0)	—
Completed rehabilitation program	5 (20.0)	0
Days to assessment		
Days since first positive COVID-19 test result	119.9 ± 16.2	129.8 ± 16.5
Days since discharge from hospital	102.3 ± 8.4	—
Symptom persistence 3-mo after COVID-19 illness		
Exertional breathlessness	17 (68.0)	21 (55.3)
Much or somewhat better	15 (60.0)	17 (44.7)
Same as during the acute phase of infection	1 (4.0)	2 (5.3)
Worse or much worse than during the acute phase of infection	1 (4.0)	2 (5.3)
Fatigue	18 (72.0)	27 (71.1)
Much or somewhat better	15 (60.0)	19 (50.0)
Same as during the acute phase of infection	2 (8.0)	7 (18.4)
Worse or much worse than during the acute phase of infection	1 (4.0)	1 (2.6)

Definition of abbreviations: BMI = body mass index; COVID-19 = coronavirus disease; ICU = intensive care unit.
Values are *n* (%) or mean ± standard deviation.

hospitalized patients. Persistent breathlessness in hospitalized patients may partly be explained by the residual impairments in TLC and D_{LCO}. Although these findings are consistent with studies that evaluated breathlessness in patients with similar lung function defects (12), we cannot rule out the confounding effects of age, obesity, and comorbid conditions on lung mechanics, which may explain some of the differences between groups. Furthermore, extrapulmonary factors likely also contributed to breathlessness during exercise, as both groups reported severe breathlessness (Borg > 6) at end-exercise despite the presence of a ventilatory reserve.

Cardiorespiratory fitness is a powerful predictor of mortality in the general population (13). It is therefore striking that >50% of our COVID-19 survivors had a peak $\dot{V}O_2$ below 85% predicted, a rate that is comparable to patients recovered from severe acute respiratory syndrome (14). The respiratory quotient >1.05 in conjunction with a

Table 2. Spirometry, lung volumes, diffusing lung capacity for carbon monoxide, transthoracic echocardiography, and measurements at the peak of symptom-limited incremental cycle CPET in hospitalized and nonhospitalized patients with COVID-19 3–4 months after infection

	Hospitalized (*n* = 25)	Nonhospitalized (*n* = 38)
Spirometry		
FEV_1, % predicted	90.3 ± 13.5	95.5 ± 14.7
FEV_1 < LLN	4 (16.0)	4 (10.5)
FVC, % predicted	88.6 ± 14.5	100.7 ± 14.3*
FVC < LLN	6 (24.0)	1 (2.6)†
FEV_1/FVC, %	76.0 ± 7.0	75.5 ± 7.8
FEV_1/FVC < LLN	1 (4.0)	6 (15.8)
Lung volumes		
TLC, % predicted	84.7 ± 14.5	95.7 ± 12.1*
TLC < LLN	12 (48.0)	3 (7.9)‡
RV, % predicted	76.5 ± 21.6	79.7 ± 17.7
RV < LLN	8 (32.0)	4 (10.5)
RV/TLC, % predicted	30.0 ± 6.8	24.0 ± 6.7‡
RV/TLC < LLN	7 (28.0)	13 (34.2)
Diffusing capacity		
D_{LCO}, % predicted	69.1 ± 14.9§	81.5 ± 15.1*
D_{LCO} < LLN	17 (70.8)§	12 (31.6)*
D_{LCO}/V_A, % predicted	90.7 ± 14.3§	96.8 ± 17.0
D_{LCO}/V_A < LLN	2 (8.3)§	4 (10.5)
Transthoracic echocardiography		
LVEF, %	63.6 ± 2.5‖	62.7 ± 3.7
LVEF < 55%	0‖	1 (2.6)
Measurements at the peak of symptom-limited incremental cycle CPET		
Work rate, % predicted	80.2 ± 24.8	99.2 ± 26.1*
$\dot{V}O_2$, % predicted	64.3 ± 19.2	83.5 ± 17.9‡
$\dot{V}O_2$% predicted <85%	20 (80.0)	21 (55.2)*
$\dot{V}CO_2$, L/min	1.73 ± 0.65	2.43 ± 0.80‡
RQ	1.24 ± 0.11	1.24 ± 0.09
RQ < 1.05	1 (4.0)	1 (2.6)
HR, % predicted	86.1 ± 15.0	97.0 ± 9.0*
O_2 pulse, % predicted	71.9 ± 19.3	81.3 ± 12.8†
HRR, %	65.4 ± 24.6	87.9 ± 18.8‡
HRR < 0.8	17 (68.0)	7 (18.4)‡
Sp_{O_2}, %	97.0 ± 1.5	97.0 ± 1.7
$\dot{V}E$, % predicted MVV	51.0 ± 13.1	57.8 ± 12.2†
$\dot{V}E/\dot{V}CO_2$, nadir	32.40 ± 5.65	29.04 ± 4.16*
IC, % predicted	80.6 ± 17.9	92.4 ± 15.9*
IRV, L	0.92 ± 0.50	1.13 ± 0.48
Symptoms, Borg scale 0–10		
Breathlessness intensity	6.8 ± 2.1	7.4 ± 2.2
Leg discomfort	7.1 ± 2.3	7.8 ± 2.1
Reason for stopping		
Breathing discomfort	3 (12.0)	12 (31.6)
Leg discomfort	13 (52.0)	17 (44.7)
Combination of breathing and legs	7 (28.0)	9 (23.7)
Other		
Anxiety	1 (4.0)	0
Knee pain	1 (4.0)	0

Definition of abbreviations: COVID-19 = coronavirus disease; CPET = cardiopulmonary exercise test; D_{LCO} = diffusing lung capacity for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity, HR = heart rate; HRR = heart rate reserve; IC = inspiratory capacity; IRV = inspiratory reserve volume; LLN = lower limit of normal; LVEF = left ventricular ejection fraction; MVV = maximum voluntary ventilation; RQ = respiratory quotient; RV = residual volume; Sp_{O_2} = oxygen saturation by pulse oximetry; TLC = total lung capacity; V_A = alveolar volume; $\dot{V}CO_2$ = carbon dioxide production; $\dot{V}E$ = minute ventilation; $\dot{V}O_2$ = oxygen consumption.
Values are *n* (%) or mean ± standard deviation.
*$P < 0.01$.
†$P < 0.05$.
‡$P < 0.001$.
§$n = 24$, one patient was unable to perform D_{LCO}.
‖$n = 24$, one patient did not complete transthoracic echocardiography.

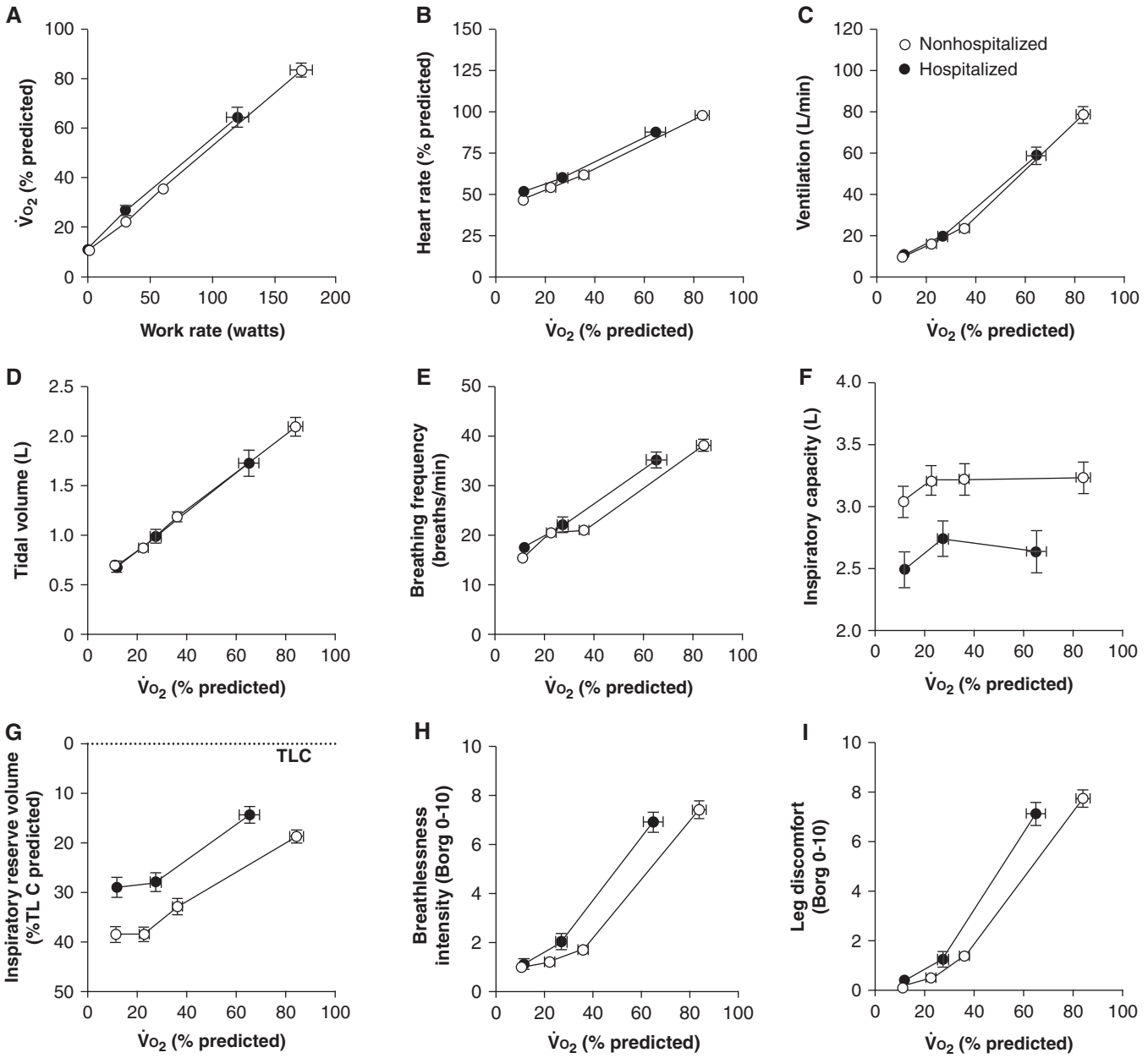

Figure 1. (*A–I*) $\dot{V}O_2$ during an incremental cycle exercise test (*A*), and heart rate (*B*), ventilation (*C*), tidal volume (*D*), breathing frequency (*E*), inspiratory capacity (*F*), inspiratory reserve volume (*G*), breathlessness intensity (*H*), and leg discomfort (*I*) for a given $\dot{V}O_2$% predicted in hospitalized and nonhospitalized patients with COVID-19 3–4 months after SARS-CoV-2 infection. Data presented at rest, iso-work rate (highest equivalent work rate completed by all patients within each group), and peak exercise. Values are mean ± standard error of the mean. COVID-19 = coronavirus disease; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; TLC = total lung capacity; $\dot{V}O_2$ = oxygen consumption.

ventilatory reserve at peak exercise suggests that cardiovascular factors were the primary cause of exercise limitation in both groups. Impaired tissue perfusion and/or skeletal muscle atrophy and dysfunction may be significant mediators of a low $\dot{V}O_2$, particularly in hospitalized patients who reported higher leg discomfort for a given $\dot{V}O_2$. This hypothesis is supported by the observed reduction in oxygen pulse in the context of a preserved ejection fraction in hospitalized patients, increasing evidence of COVID-19–related microvascular injury in various organs and the effects of critical illness on muscle wasting (15). Furthermore, compromised oxygen use at the peripheral muscles may exacerbate symptom perception, which may result in the early attainment of intolerable breathlessness and premature termination of exercise (16, 17). Physical deconditioning and concurrent comorbid conditions likely also contributed to the reduction in peak $\dot{V}O_2$ in hospitalized patients. Finally, poor cardiorespiratory fitness in hospitalized patients may have preceded SARS-CoV-2 infection (18).

We provide the first report of CI in patients recovering from COVID-19. The lower peak $\dot{V}O_2$ and heart rate in hospitalized versus

nonhospitalized patients in the setting of a comparable peak respiratory quotient suggests that CI contributed to exercise limitation. The source of CI is unknown but may be due to the high prevalence of comorbid conditions in hospitalized patients, or it may be secondary to patients becoming breathless and terminating exercise before achieving a maximal heart rate response.

Limitations of this study include a small sample size, lack of premorbid baseline information, and absence of matched control groups. Therefore, we cannot be certain if the physiologic abnormalities in our patients preceded or followed SARS-CoV-2 infection. Given the important differences in the demographic and clinical makeup of our study groups, we could not adequately assess the confounding effects that preexisting comorbidities could have on our observations. Finally, we caution against the generalizability of our results given the small sample size and use of Canadian reference values (8–10).

In conclusion, we demonstrate mild impairments in lung volumes and gas exchange and a diminished functional capacity 3–4 months after discharge from hospital with SARS-CoV-2 infection, which occurred in the presence of a preserved left ventricular ejection fraction. Investigations into the effects of COVID-19 on peripheral muscle structure, perfusion, and function are warranted. Additional studies are required to understand the mechanisms of breathlessness after SARS-CoV-2 infection, particularly in patients not requiring hospitalization. ■

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Tissue Plasminogen Activator in Critically Ill Adults with COVID-19

To the Editor:

Hypercoagulability may be a key factor leading to multiorgan failure and death in critically ill patients with coronavirus disease (COVID-19) (1). Extensive pulmonary microthrombi have been described in patients with acute respiratory distress syndrome from COVID-19 (2, 3). These observations have prompted some clinicians to advocate for the use of fibrinolytic therapy with recombinant tissue plasminogen activator (tPA) in select critically ill patients with COVID-19 (4, 5), yet sparse data on safety and efficacy are available (6, 7).

We used data from STOP-COVID (Study of the Treatment and Outcomes in Critically Ill Patients with COVID-19), a multicenter cohort study of critically ill adults with COVID-19 admitted to 68 geographically diverse hospitals across the United States, to examine the safety and efficacy of tPA in this setting (8). We included patients from the STOP-COVID registry admitted to intensive care units (ICUs) between March 1 and July 1, 2020, who received tPA for confirmed pulmonary embolism (PE) or suspected PE or pulmonary microthrombi within 14 days after ICU admission. Patients were followed until hospital discharge or death.

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Author Contributions: D.J.D., S.S., J.R., and D.E.L. conceived the study, had full access to the data in the study, and take responsibility for the integrity of the data and accuracy of the analyses. D.J.D. and D.E.L. wrote the manuscript. D.J.D., I.P., and D.E.L. designed the table and figure. D.J.D., S.S., S.K.B., and D.E.L. acquired the data. All authors provided feedback on the protocol and critically revised and approved the final version of the manuscript.

The primary safety endpoint was major bleeding within 7 days of tPA administration, defined as bleeding within a critical area or organ (e.g., intracranial, retroperitoneal, pericardial, or intramuscular bleeding with compartment syndrome) or bleeding requiring a procedural intervention (9). The primary efficacy endpoint was change in the ratio of partial pressure of arterial oxygen to fraction of inspired oxygen (Pa_{O_2}:FI_{O_2}) before and after tPA administration. Secondary efficacy endpoints were the proportion of patients who required therapies for refractory hypoxemia (prone position, neuromuscular blockade, or inhaled pulmonary vasodilators), the proportion of patients with an increase in the Pa_{O_2}:FI_{O_2} ratio ⩾50% after tPA administration, and the change in the vasoactive-inotropic score (VIS) in the first 24 hours after tPA administration (10–12). We collected data on the Pa_{O_2}:FI_{O_2} ratio from the closest arterial blood gas obtained within 48 hours before tPA and the first three arterial blood gases within 48 hours after tPA receipt. We collected VIS data immediately before and at 6, 12, and 24 hours after tPA receipt.

Among 5,154 patients enrolled in STOP-COVID, 93 (1.8%) received tPA. We excluded patients who received tPA for intracatheter thrombosis ($n = 28$), peripheral arterial thrombosis ($n = 2$), ischemic stroke ($n = 2$), myocardial infarction ($n = 1$), or catheter-directed thrombolysis ($n = 1$), leaving a total of 59 patients (from 16 institutions) included in this analysis.

Baseline characteristics of these 59 patients (1.1% of the parent cohort) are shown in Table 1. The median age was 60 years (interquartile range [IQR], 50–67), 43 (72.9%) were male, and 19 (32.2%) were White. A total of 58 patients (98.3%) were receiving invasive mechanical ventilation at the time of tPA administration, 43 (72.9%) were receiving vasoactive medications, and 8 (13.6%) were receiving renal replacement therapy for acute kidney injury. The median Pa_{O_2}:FI_{O_2} ratio at the time of tPA receipt was 86 (IQR, 69–157), and 30 patients (50.8%) were receiving at least one therapy for refractory hypoxemia. PE was radiologically confirmed in 12 patients (20.3%); the remaining 47 patients (79.7%) had suspected PE or pulmonary microthrombi. Six patients (10.2%) received tPA during a cardiac arrest, and all six of these patients died. The median time from ICU admission to tPA administration was 4 days (IQR, 1–8), the median total dose of tPA was