Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eMethods

Endpoint definitions

Ventilator-free days (VFD). VFD to day 28 was defined as the number of days of unassisted breathing to day 28 after randomization, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient returned to assisted breathing and subsequently achieved unassisted breathing prior to day 28, VFD was counted from the end of the last period of assisted breathing to day 28 unless the period of assisted breathing was less than 24 hours and the purpose of assisted breathing was a surgical procedure. If the patient was receiving assisted ventilation at day 28 or died prior to day 28, VFDs were set to 0. Individuals who went on comfort care but were alive at day 28 were given a VFD score of 0 since they had no VFDs prior to the time of comfort care initiation. Individuals who were known to be alive at day 28 but had unknown day 28 ventilation status were assigned a VFD of zero (N=10). This post-hoc modification to the VFD definition was made to accommodate individuals who were discharged to long-term care while ventilated where information on ventilation status was unobtainable.

Unassisted breathing was defined as the patient breathing spontaneously with a face mask, nasal prong oxygen, or on room air, T-tube breathing, tracheostomy mask breathing, or CPAP < 5 without pressure-support or intermittent mandatory ventilation, or with the use of noninvasive ventilation solely for sleep-disordered breathing. Assisted breathing was defined as any level of ventilatory support at pressures higher than the unassisted breathing thresholds.

ICU-free days. ICU free days to day 28 after randomization were defined in a similar fashion to VFDs. If an individual died at any point during the 28-day follow-up

period or if the person was not discharged from the ICU by day 28, they were assigned an ICU-free day score of 0. Individuals who went on comfort care but were alive at day 28 were given a ICU-free day score of 0 since they were in the ICU at the time of comfort care initiation. Otherwise, the ICU-free day score was calculated as the remaining time from the last recorded ICU discharge date to day 28. Partial days were considered.

Total ventilator free days (TVFD): Total ventilator free days were defined as the number of days (≥24-hour periods) that a person was off ventilator during the study. It includes VFD plus any ≥24-hour intermittent ventilator free periods that the individual was off ventilation. For individuals who died or went on comfort care, TVFDs were counted until initiation of comfort care or time of death if no comfort care was reported.

Ventilator-associated pneumonia: Ventilator-associated pneumonia was defined as pneumonia recorded while the individual was intubated that occurred at least 24 hours after initial intubation.

Pressor use: Pressor use was defined as any recorded usage of Norepinephrine, Vasopressin, Epinephrine, or Phenylephrine on daily assessment forms.

Sedative use: Sedative use was defined as any recorded usage of Benzodiazepines, Propofol, Dexmedatomidine, Haloperidol, Quetiapine, or Phenobarbital on daily assessment forms.

Development of bilateral or diffuse infiltrates: Infiltrate assessment and classification was performed locally. Analyses of infiltrates used any available X-ray or CT scan information. If both CT scan and X-ray data were available, the CT scan data was preferred.

Development of PaO_2/F_IO_2 ratios consistent with ARDs and bilateral or diffuse infiltrates: An individual was considered as having bilateral or diffuse infiltrates and PaO_2/F_IO_2 ratio below a certain threshold at the same time if bilateral or diffuse infiltrates were recorded within 2 days of the arterial blood gas (ABG) reading. The date the bilateral or diffuse infiltrates were recorded was used as the timing of the event.

Statistical considerations

Sample size

We initially estimated a need to enroll 916 patients based on the same assumptions as the sample size calculation in the EDEN and FACTT studies (1, 2): trial power of 90%, two-sided alpha level of 0.05, the assumption that the SD for VFDs would be 10.5, and the assumption that the absolute difference in VFDs between individuals randomized to the intervention arm versus usual care would be 2.25. As a result of the first planned interim analysis (December 14, 2018) the Data and Safety Monitoring Board (DSMB) recommended that the Data Coordinating Center (DCC) recalculate the sample size. Based on the observed values for the VFD in the usual care group (SD of 9.9), a power of 80%, and a withdrawal rate of 1% (which was not accounted for in the initial sample size estimate but was observed during the first planned interim analysis) the DCC estimated the need to enroll 544 patients.

Interim analyses

Two formal interim analyses were conducted: the first when approximately 1/3 of the initial total patients had been evaluated (December 14, 2018), and the second when approximately 2/3 had been evaluated (August 13, 2021). At the first interim analysis

the DSMB requested a sample size recalculation (see section above). The protocol was officially changed with the new sample size on February 9, 2020. At the second interim analysis, there were no statistical concerns for futility or proof of hypothesis.

The monitoring boundaries for these 'looks' at the data were based on the Lan-DeMets 'alpha spending function' approach. This yields an overall significance level of approximately 0.05. We chose monitoring boundaries in the 'Pocock' family (3,4) using 'ld98', an interactive program based on the research of K.K. Gordon Lan and David DeMets. See the protocol for more details on monitoring boundaries.

Analyses

The primary analysis of the difference in VFDs between the intervention and usual care arms was based on the Wilcoxon rank-sum statistic. Fine and Gray competing risk regression (4) with death as the competing risk was used to compare time to successful extubation between treatment groups. Individuals who were discharged on ventilator or who had unknown 28-day vital status were censored at their discharge date. Individuals who went on comfort care but were alive at day 28 were censored at day 28. Linear least-squares regression with robust standard errors was used to compare VFDs, TVFD, and ICU-free days between treatment arms. Occurrence of severe adverse events and all-cause mortality by day 28 were analyzed using logistic regression models, unless otherwise specified.

Kaplan–Meier survival curves and Cox models were used to compare 1) time to death, 2) time to development of bilateral or diffuse infiltrates, 3) time to ABG measurements consistent with severe ARDS, and 4) time to ABG measurements

consistent with severe ARDS and bilateral or diffuse infiltrates between treatment arms. For 1) individuals were censored at their last known alive date if vital status at day 28 was unknown, or at day 28. For 2), individuals were censored at the date of the last recorded X-ray or CT scan. Only individuals who had imaging (X-ray or CT scan) conducted during the initial assessment were included in the analysis. For 3) individuals were censored at the last recorded ABG reading. Only individuals who had ABGs recorded prior to randomization were included in the analysis. For 4), individuals were censored at the date of the last recorded X-ray or CT scan with an ABG measurement within +/- 2 days. Only individuals who had imaging conducted during the initial assessment and ABGs recorded prior to randomization were included in the analysis.

We performed post-hoc subgroup analysis on the primary outcome by testing treatment by subgroup interactions for sex, smoking history (current/former, never, or unknown), BMI (<30 and ≥ 30), age (<41and ≥41 years, the median age), injury severity score (<29 and ≥29, the median score), PaO_2/F_IO_2 ratio (>300 and ≤300 mm Hg), and absence or presence of inclusion criteria risk factors for ARDS (traumatic brain injury, >1 long bone facture, shock, lung contusion, >6 units of blood) using linear least-squares regression models with robust standard errors.

Adjusted models included age, sex, smoking history, traumatic brain injury, > 1 long bone fracture, shock, lung contusion, receipt of > 6 units of blood products in the first 24 hours of care, injury severity score, PaO_2/F_IO_2 ratio ≤ 300 mm Hg prior to randomization, and trial center (adjusted Cox models were stratified by trial center). Missing values for PaO_2/F_IO_2 ratio, and injury severity score were imputed using

multivariate imputation by chained equations with predictive mean matching. Auxiliary variables included in the imputation included age, sex, smoking history, inclusion risk factor criteria, clinic, F_IO_2 and PaO_2 within 24-hours after randomization, and time from randomization to ABG measurements. Results were pooled across the 50 imputations using Rubin's rules (6) for computing the total variance. All analyses are based on the intention-to-treat principle.

eReferences

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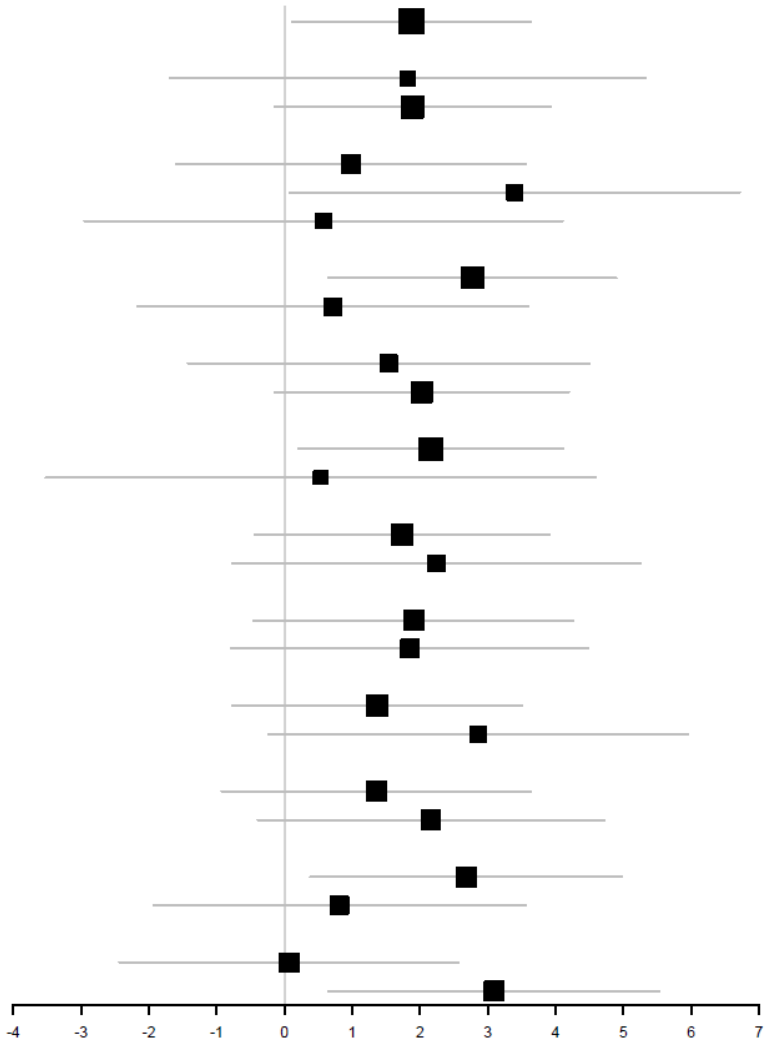
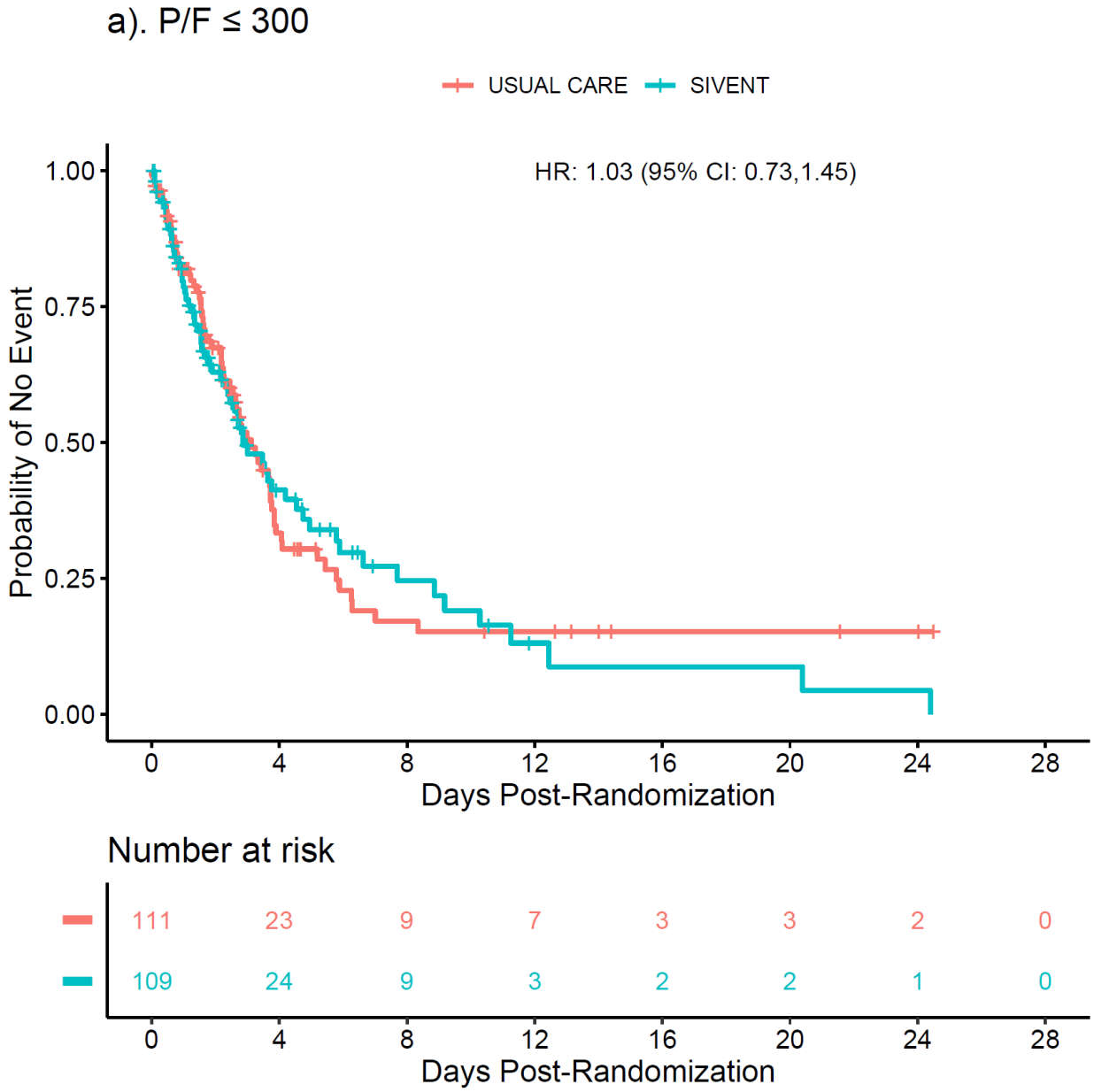
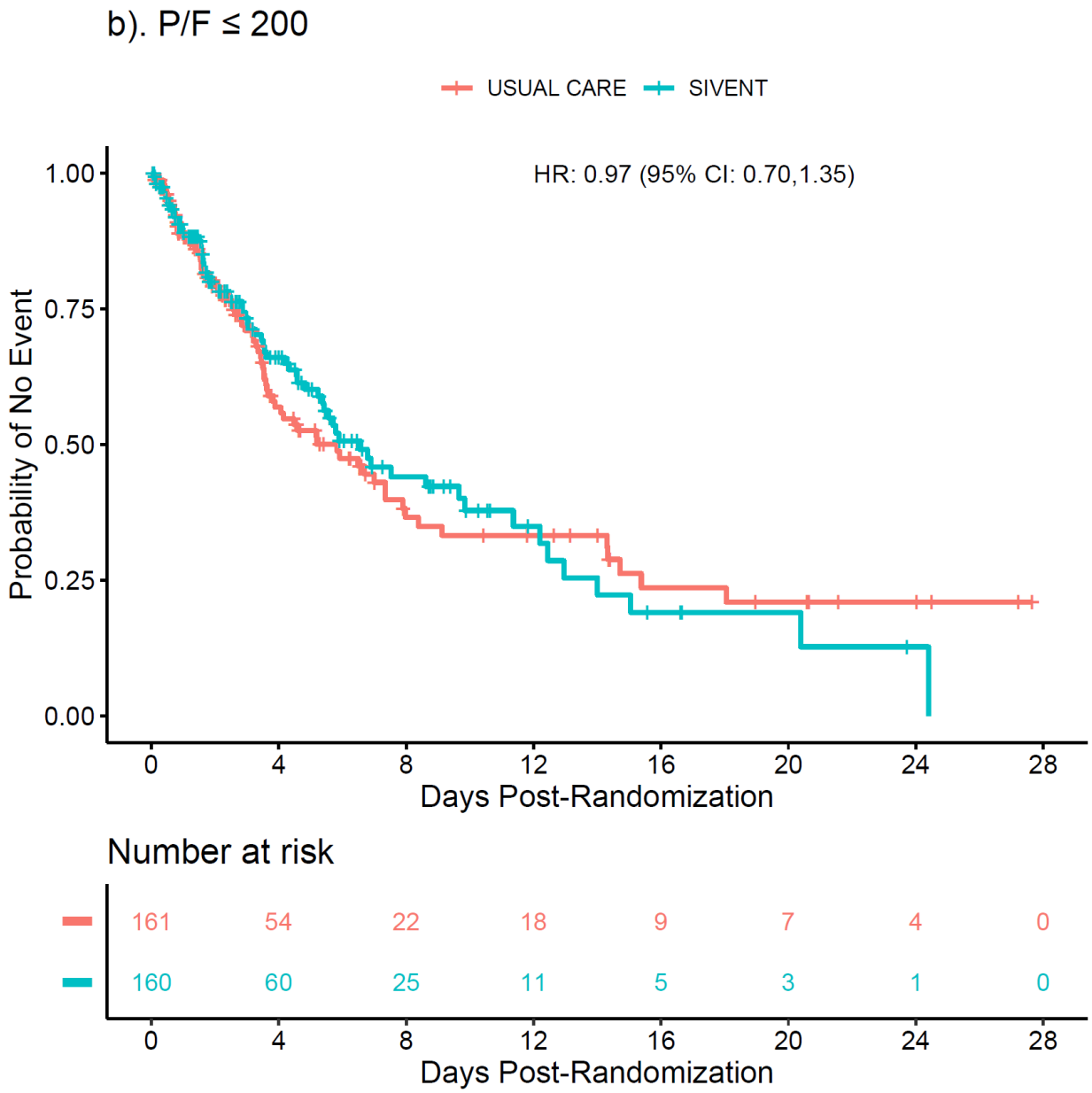
eFigure 1. Relationship between treatment assignment and VFDs in patient subgroups. Estimated difference in VFD and 95% confidence intervals, sighs vs. usual care. Estimates greater than 0 favor receiving sighs.

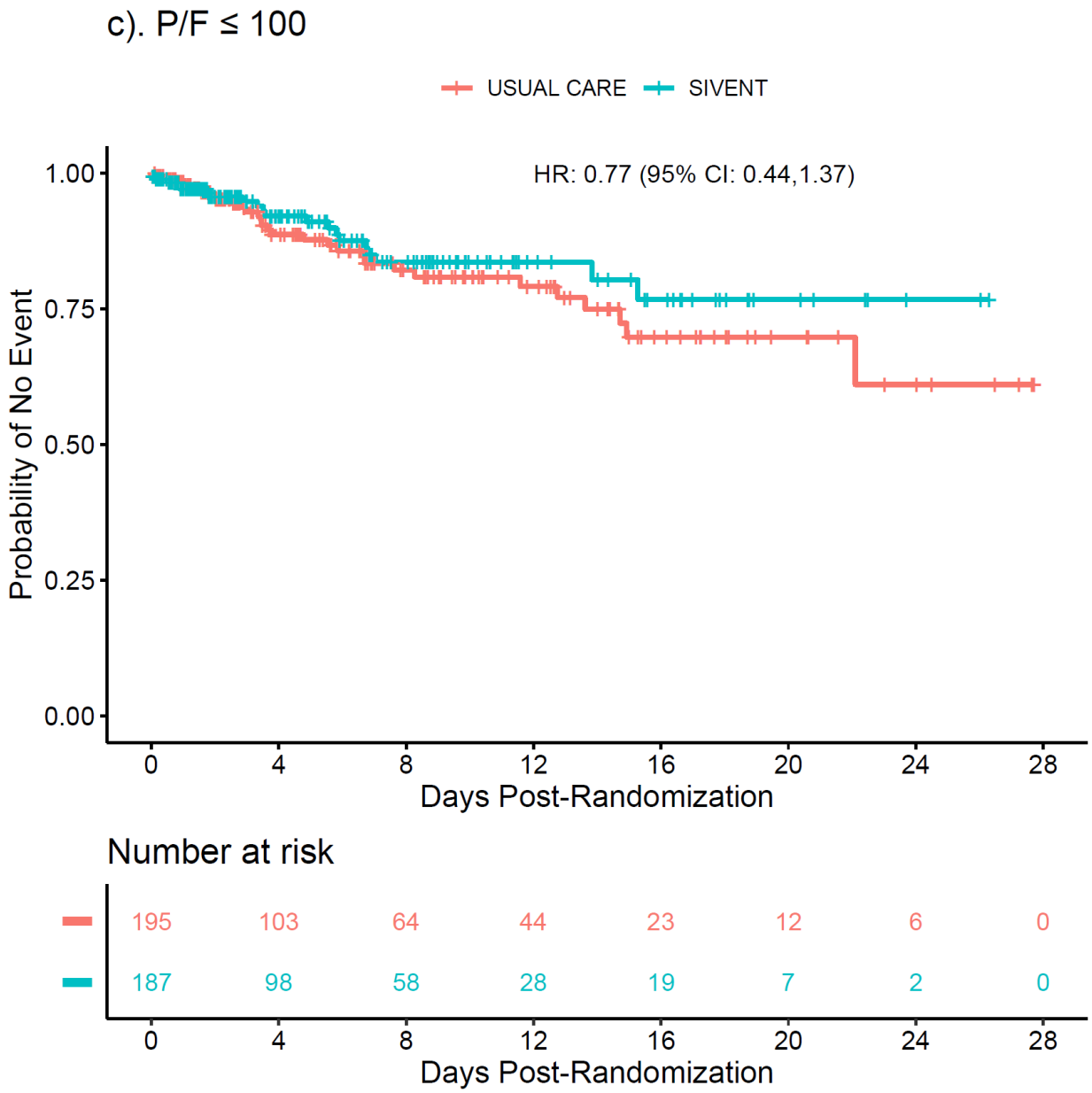
Subgroups	N(%)	Estimate (95% CI)	P-value
Overall	520	1.9 (0.11, 3.64)	0.04
Sex			0.97
female	130 (24.8%)	1.8 (-1.69, 5.33)	
male	394 (75.2%)	1.9 (-0.15, 3.92)	
Smoking History			0.43
Current/Former	237 (45.2%)	1 (-1.59, 3.56)	
Never	145 (27.7%)	3.4 (0.08, 6.71)	
Unknown	142 (27.1%)	0.6 (-2.95, 4.1)	
BMI			0.26
<30	330 (63%)	2.8 (0.65, 4.89)	
≥ 30	194 (37%)	0.7 (-2.17, 3.6)	
TBI			0.79
no	200 (38.2%)	1.5 (-1.42, 4.5)	
yes	324 (61.8%)	2 (-0.15, 4.19)	
>1 long bone facture			0.48
no	433 (82.6%)	2.2 (0.2, 4.11)	
yes	91 (17.4%)	0.5 (-3.52, 4.58)	
Shock			0.79
no	347 (66.2%)	1.7 (-0.44, 3.9)	
yes	177 (33.8%)	2.2 (-0.77, 5.25)	
Lung contusion			0.98
no	306 (58.4%)	1.9 (-0.46, 4.26)	
yes	218 (41.6%)	1.8 (-0.79, 4.48)	
>6 units of blood			0.44
no	341 (65.1%)	1.4 (-0.78, 3.5)	
yes	183 (34.9%)	2.9 (-0.24, 5.95)	
Age			0.65
<41	261 (49.8%)	1.4 (-0.93, 3.64)	
≥41	263 (50.2%)	2.2 (-0.4, 4.72)	
P/F*			0.31
> 300	258 (56.3%)	2.7 (0.38, 4.97)	
≤ 300	200 (43.7%)	0.8 (-1.94, 3.56)	
ISS*			0.09
<29	249 (48.3%)	0.1 (-2.43, 2.57)	
≥29	266 (51.7%)	3.1 (0.64, 5.53)	

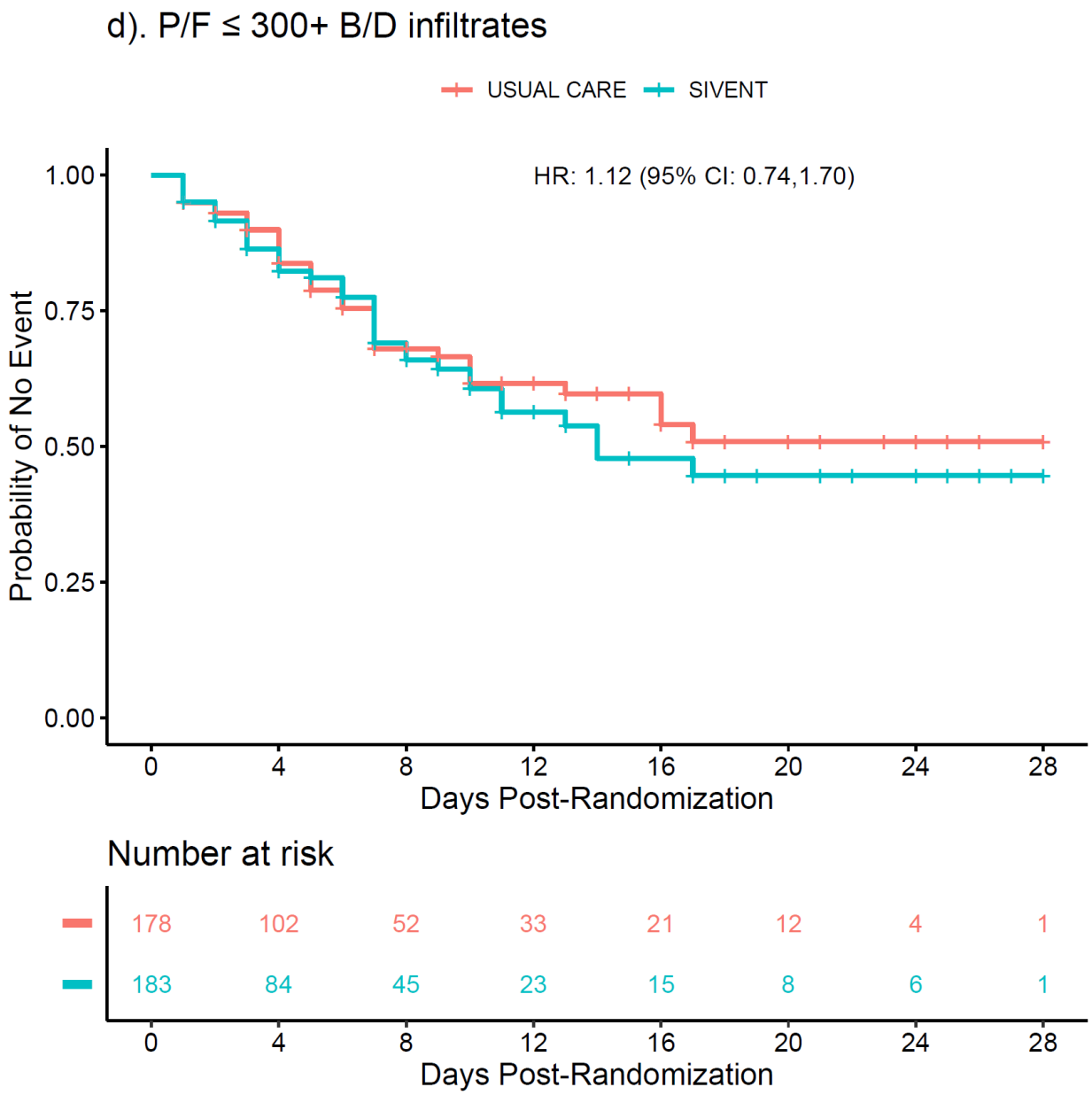


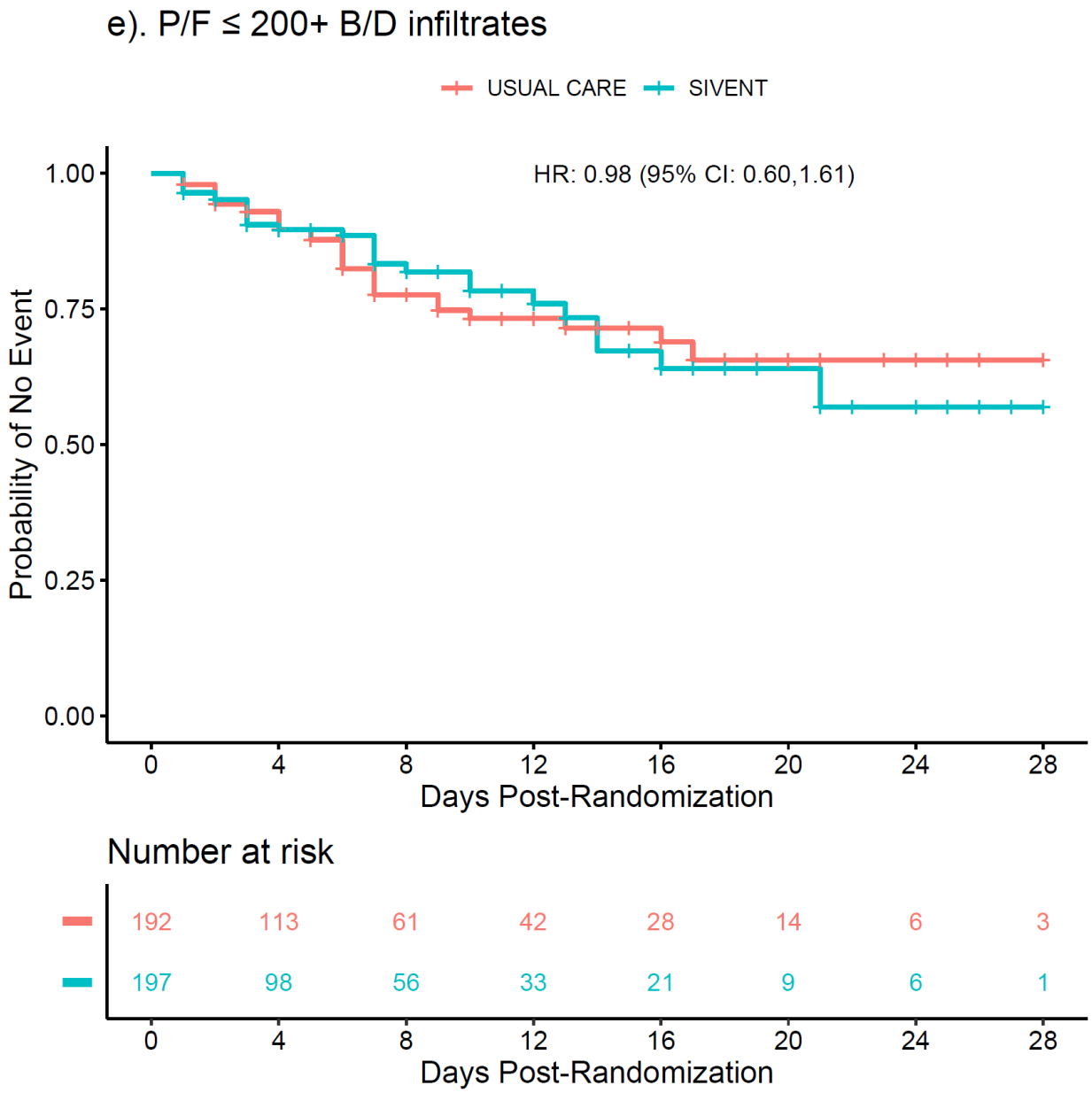
eFigure 2: Kaplan–Meier estimate of time to development of a) P/F ≤300, b) P/F ≤ 200, c) P/F ≤ 100, d) P/F ≤300 and bilateral/diffuse infiltrates, e) P/F ≤ 200 and bilateral/diffuse infiltrates, f) P/F ≤ 100 and bilateral/diffuse infiltrates, and g) bilateral or diffuse infiltrates. Hazard Ratio (HR) and 95% Confidence Interval (95% CI) are also displayed. A HR greater than 1 is interpreted as greater hazard of event for individuals randomized to sighs.

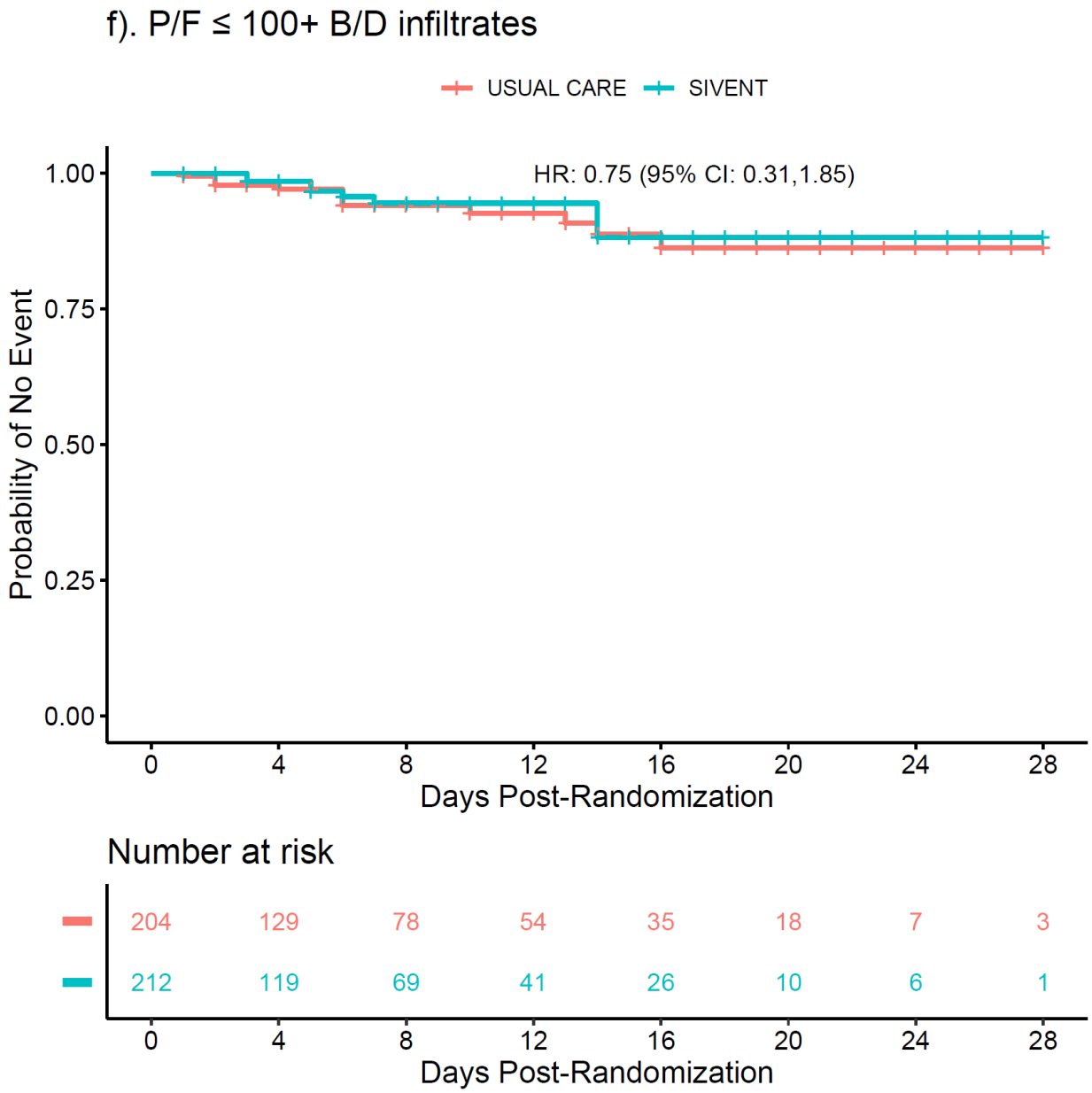


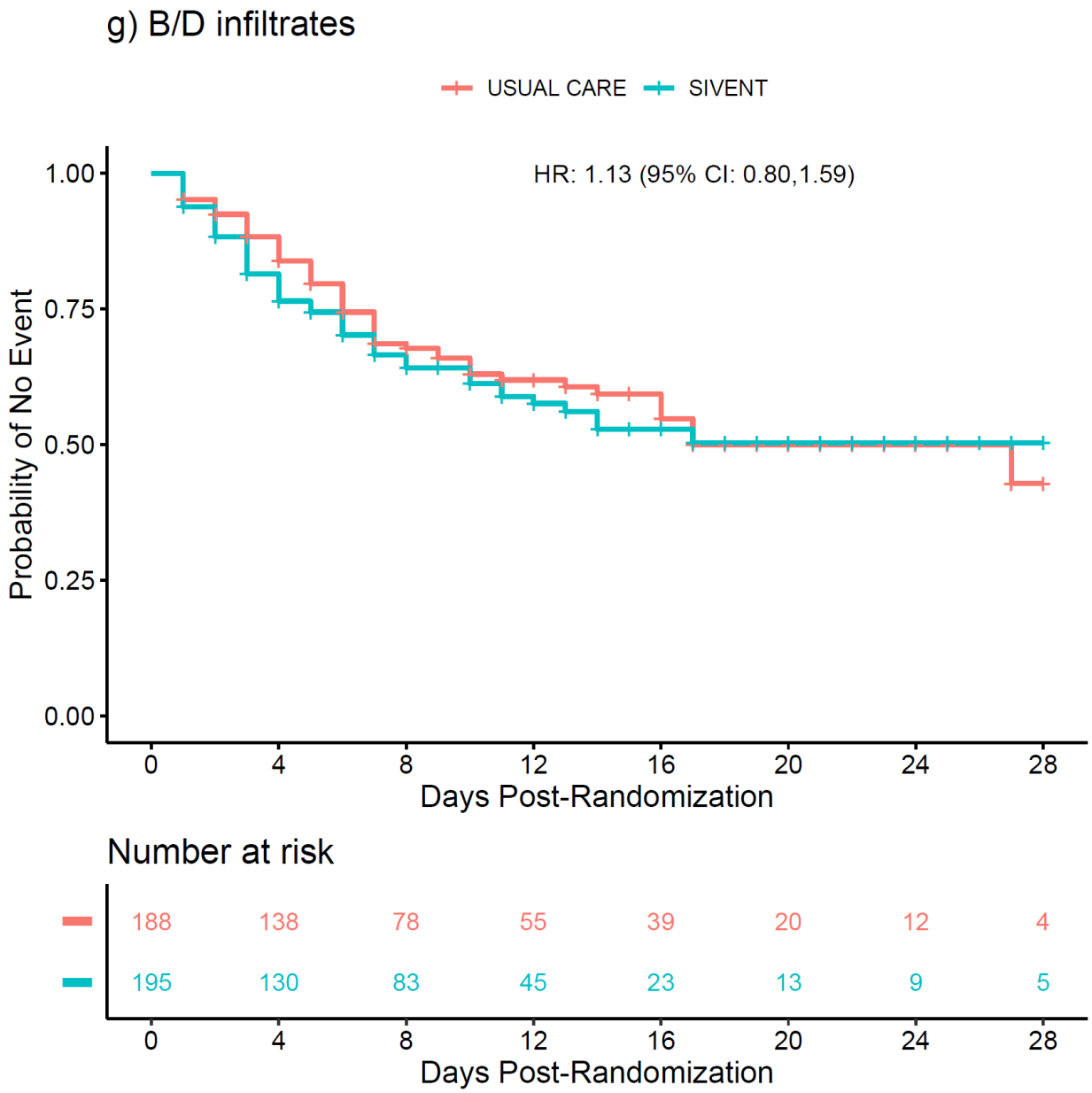












eTable 1: Ventilator mode and Richmond Agitation-Sedation Scale during follow-up by treatment assignment.
Information was collected daily while the participant was in the ICU and while they continued to receive ventilation.

	Day 1		Day 3		Day 5		Day 7		Day 14		Day 21		Day 28	
	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care	Usual Care + Sighs	Usual Care
N	259	263	241	252	217	218	187	181	110	126	53	69	30	36
On mechanical ventilation, N(%)	257 (99.2%)	262 (99.6%)	192 (79.7%)	201 (79.8%)	155 (71.4%)	158 (72.5%)	125 (66.8%)	133 (73.5%)	58 (52.7%)	82 (65.1%)	31 (58.5%)	35 (50.7%)	13 (43.3%)	16 (44.4%)
Mode, N(%)														
AMV	96 (37.4%)	96 (36.6%)	65 (33.9%)	63 (31.3%)	49 (31.6%)	57 (36.1%)	36 (29.0%)	43 (32.3%)	16 (27.6%)	18 (22.0%)	7 (22.6%)	9 (25.7%)	5 (38.5%)	4 (25.0%)
CMV	65 (25.3%)	57 (21.8%)	36 (18.8%)	37 (18.4%)	26 (16.8%)	25 (15.8%)	18 (14.5%)	15 (11.3%)	3 (5.2%)	9 (11.0%)	2 (6.5%)	2 (5.7%)	1 (7.7%)	0 (0.0%)
CPAP	4 (1.6%)	11 (4.2%)	18 (9.4%)	25 (12.4%)	17 (11.0%)	20 (12.7%)	11 (8.9%)	19 (14.3%)	9 (15.5%)	13 (15.9%)	1 (3.2%)	6 (17.1%)	1 (7.7%)	3 (18.8%)
PCV	42 (16.3%)	37 (14.1%)	33 (17.2%)	27 (13.4%)	29 (18.7%)	22 (13.9%)	27 (21.8%)	17 (12.8%)	14 (24.1%)	13 (15.9%)	8 (25.8%)	7 (20.0%)	3 (23.1%)	5 (31.2%)
PSV	9 (3.5%)	26 (9.9%)	19 (9.9%)	24 (11.9%)	23 (14.8%)	16 (10.1%)	24 (19.4%)	17 (12.8%)	11 (19.0%)	20 (24.4%)	10 (32.3%)	7 (20.0%)	2 (15.4%)	3 (18.8%)
SIMV	41 (16.0%)	33 (12.6%)	17 (8.9%)	20 (10.0%)	8 (5.2%)	10 (6.3%)	6 (4.8%)	11 (8.3%)	2 (3.4%)	5 (6.1%)	2 (6.5%)	2 (5.7%)	1 (7.7%)	0 (0.0%)
Other	0 (0.0%)	2 (0.8%)	4 (2.1%)	5 (2.5%)	3 (1.9%)	8 (5.1%)	2 (1.6%)	11 (8.3%)	3 (5.2%)	4 (4.9%)	1 (3.2%)	2 (5.7%)	0 (0.0%)	1 (6.2%)
Tidal Volume (mL), mean (SD)	494.4 (93.1)	511.0 (111.4)	500.1 (109.8)	511.5 (113.3)	500.7 (118.2)	517.2 (111.8)	499.1 (118.0)	516.4 (119.6)	483.3 (99.4)	498.8 (128.9)	527.2 (149.3)	516.4 (155.5)	468.8 (106.9)	574.5 (122.2)
Tidal Volume/ PBW (mL/kg)	7.2 (1.2)	7.5 (1.7)	7.4 (1.6)	7.4 (1.6)	7.4 (1.8)	7.6 (1.5)	7.4 (1.7)	7.6 (1.6)	7.4 (1.5)	7.4 (2.0)	7.9 (2.1)	7.3 (2.1)	7.0 (1.5)	8.0 (2.2)
RASS, median [IQR]	-2 [-3, -1]	-2 [-4, -1]	-1 [-3, 0]	-1 [-3, 0]	-1 [-3, 0]	-1 [-3, 0]	-1 [-2, 0]	-1 [-3, 0]	0 [-2, 0]	0 [-2, 0]	-1 [-2, 0]	0 [-1, 0]	0 [-1, 0]	0 [-1, 0]

AMV: Assisted Mechanical Ventilation; CMV: Continuous Mandatory Ventilation; CPAP: Continuous Positive Airway Pressure; PCV: Pressure Control Ventilation; PSV; SMIV: Synchronized Intermittent Mandatory Ventilation; PBW: Predicted Body Weight; RASS: Richmond Agitation-Sedation Scale

eTable 2: Study outcomes for complete case adjusted[a] analyses.

	Estimate (95% CI) Usual Care + Sighs vs Usual Care
Primary	
VFDs	
Overall[b]	1.6 (-0.1, 3.3)
Death excluded[c]	1.0 (-0.8, 2.7)
Secondary	
ICU-free days	
Overall[b]	0.8 (-0.8, 2.4)
Death excluded[c]	0.2 (-1.4, 1.9)
TVFD	
Overall[b]	1.6 (-0.1, 3.2)
Death excluded[c]	0.9 (-0.7,2.5)

VFD = Ventilator Free Days; ICU-Free Days = Intensive Care Unit Free Days; TVFD = Total Ventilator Free Days

[a]Models were adjusted for age, sex, smoking history, traumatic brain injury, > 1 long bone fracture, shock, lung contusion, receipt of > 6 units of blood products in the first 24 hours of care, injury severity score, PaO_2/F_IO_2 ratio ≤ 300 mmHg prior to randomization, and trial center. Only individuals not missing information for any of these characteristics in the analysis.

[b]N = 222 for Usual Care, N = 226 for Usual Care + Sighs

[c]N = 180 for Usual Care, N = 199 for Usual Care + Sighs

eTable 3: Lowest observed partial pressure of oxygen to the fraction of inspired oxygen (P/F) ratio during follow-up for individuals without P/F ratios consistent with ARDS (P/F>300) at baseline.

	Usual Care + Sighs	**Usual Care**
P/F > 300 on enrollment, N	130	128
Lowest P/F on follow-up, Mean (SD)	270.3 (140.0)	263.6 (122.2)
Lowest P/F on follow-up, N (%)		
> 300	46 (35.4%)	44 (34.4%)
≤ 300	63 (48.5%)	67 (52.3%)
>200 to ≤ 300	22 (16.9%)	26 (20.3%)
100 to ≤ 200	29 (22.3%)	32 (25.0%)
< 100	12 (9.2%)	9 (7.0%)

eTable 4: Status at Discharge

Discharge Status, N (%)	Usual Care + Sighs (N = 261)	Usual Care (N = 263)
Deceased by day 28[a]	30 (11.6)	46 (17.6)
Discharged to extended care facility, off ventilator[b]	101 (38.7)	89 (33.8)
Discharged to extended care facility, on ventilator[b]	6 (2.3)	5 (1.9)
Discharged home	41 (15.7)	49 (18.6)
Not discharged by day 28	79 (30.3)	71 (27.0)
Other	2 (0.8)	1 (0.4)
Unknown[c]	2 (0.8)	2 (0.8)
New prescription for O_2 at discharge[d]	20 (7.7)	12 (4.6)

[a]Two individuals (1 Usual Care, 1 Usual Care + Sighs) were discharged to hospice and died prior to day 28.
[b]Extended care facilities defined as: skilled nursing facilities, rehab, and LTAC
[c]Withdrawals and unknown day 28 status.
[d]Individuals who were discharged but later died or who had unknown day 28 vital status are included in this analysis.