

# Sigh in Patients With Acute Hypoxemic Respiratory Failure and ARDS

## The PROTECTION Pilot Randomized Clinical Trial

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## **e-Appendix 1.**

### **ADDITIONAL METHODS**

**Exclusion criteria.** Age younger than 18 years;  $\text{PaO}_2/\text{FiO}_2$  ratio  $\leq 100$  mmHg or PEEP  $\geq 15$  cmH<sub>2</sub>O or  $\text{PaCO}_2 > 60$  mmHg or arterial pH  $< 7.30$ ; known neuro-muscular or central nervous system disorder; history of severe chronic obstructive pulmonary disease or fibrosis; AHRF or ARDS fully explained by cardiac failure or fluid overload; evidence of active air leak from the lung; cardiovascular instability; clinical suspicion of elevated intracranial pressure; extra-corporeal life support (i.e., extra-corporeal membrane oxygenation); moribund status (i.e., patient deemed at extremely high risk of dying within hours); refusal by the attending physician.

**Rescue treatments.** In case of desaturation with  $\text{SpO}_2 \leq 90\%$ , after ruling out hemodynamic impairment, airway obstruction and ventilator malfunction, the following rescue step-up strategy was allowed: institution of protective controlled mechanical ventilation and then a recruitment maneuver; PEEP increase  $\geq 15$  cmH<sub>2</sub>O; prone positioning; inhaled nitric oxide; extra-corporeal membrane oxygenation. Patients who underwent rescue treatments were re-assessed at least every 8 hours and switched back to Sigh or No Sigh group as soon as pre-defined criteria for improvement were met.

**Standard of care.** In all patients, standard of care for intubated AHRF and ARDS patients (e.g., early appropriate etiologic therapy, restrictive fluid strategy, suctioning of secretions, prophylaxis of gastric stress ulcer and deep veins thrombosis, semi-recumbent positioning, respiratory physiotherapy, adequate nutrition, monitoring of sedation, pain and delirium, tracheostomy, non-invasive respiratory support after extubation) was granted throughout the whole ICU stay in accordance to local protocols.

**Predictors of mortality.** The following exploratory analysis was performed: multivariate regression for independent predictors of mortality and ventilator-free days including classification of being responder or non-responder to Sigh. We did a preliminary evaluation of mortality and ventilator-free days (VFDs), exploring factors that might influence the two outcomes and considering possible confounders. Cox regression models for mortality and Poisson regression models for VFDs were used. Explanatory variables evaluated were: age, sex, number of comorbidities, baseline SOFA and SAPS II scores, Sigh Responder status, diagnosis of ARDS and treatment arm (Sigh or No Sigh).

### **ADDITIONAL RESULTS**

**Multivariate analyses.** The multivariate cox-regression analysis showed that the predictors of mortality were age (HR 1.045, 95% CI 1.020-1.070,  $p < 0.001$ ) and SAPSII (HR 1.026, 95% CI 1.008-1.044,  $p = 0.005$ ). Age (Beta -0.009,  $p < 0.001$ ), SOFA (Beta -0.011,  $p = 0.020$ ), Sigh responder status (Beta 0.135,  $p < 0.001$ ) and diagnosis of ARDS (Beta -0.276,  $p < 0.001$ ), instead, predicted the number of ventilator-free days.

**e-Table 1. Sigh Responders - Baseline characteristics**

	Sigh (N=73)	No Sigh (N=83)	P Value <sup>a</sup>
Demographics			
Male, No.(%)	44 (60)	54 (65))	0.537
Age, mean (SD),y	62 (18)	63 (15)	0.613
Height, median (Q1, Q3), cm	170 (165, 175)	170 (160,176)	0.466
Weight, median (Q1, Q3), Kg	80 (68, 92)	79 (65, 88)	0.337
BMI, median (Q1, Q3), Kg/m <sup>2</sup>	26.1 (23.4, 29.7)	26.2 (24.2-31.1)	0.524
Comorbidities, No.(%)			
Chronic cardiovascular disease	34 (47)	47 (57)	0.210
Chronic pulmonary disease	13 (18)	18 (22)	0.545
Diabetes	17 (23)	18 (22)	0.811
Chronic renal disease	8 (11)	13 (16)	0.390
Cancer	9 (12)	10 (12)	0.957
Number of comorbidities, No.(%)			
0	25 (34)	24(29)	0.725
1	26 (36)	27 (33)	
2	13 (18)	20 (24)	
≥3	9 (12)	12 (15)	
Recent medical history			
In-hospital days, median (Q1, Q3)	5 (3, 9)	5 (3, 8)	0.368
ICU days, median (Q1, Q3)	3 (2,5)	3 (2, 5)	0.471
Intubation days, median (Q1, Q3)	3 (2, 5)	3 (2, 4)	0.306
SAPS II, median (Q1, Q3)	42 (32, 55)	41 (31, 56)	0.869
SOFA, median (Q1, Q3)	7 (5, 10)	7 (5, 9)	0.479
RASS, No. (%)			
-2	38 (52)	47 (56)	0.843
-1	18 (25)	18 (22)	
0	17 (23)	18 (22)	

Diagnosis of sepsis, No. (%)			
Sepsis	23 (32)	25 (30)	0.352
Septic Shock	10 (14)	19 (23)	
Non septic	37 (51)	37 (45)	
Not Specified	3 (4)	2 (2)	
Etiology			
Pneumonia, No. (%)	44 (60)	47 (57)	0.645
Aspiration of gastric content, No. (%)	8 (11)	9 (11)	0.982
Vasculitis, No. (%)	1 (1)	0 (0)	0.468
Non-pulmonary sepsis, No. (%)	15 (21)	15 (18)	0.695
Trauma, No. (%)	1 (1)	4 (5)	0.960
Pancreatitis, No. (%)	3 (4)	3 (4)	1.000
Burns, No. (%)	0(0)	1 (1)	1.000
TRALI, No. (%)	3 (4)	3 (4)	1.000
Others, No. (%)	11 (15)	12 (15)	0.915
Pulmonary infiltrates, No. (%)			
None	14 (20)	13 (16)	0.726
Unilateral	23 (32)	24 (29)	
Bilateral (ARDS diagnosis)	36 (49)	46 (55)	
PEEP, median (Q1, Q3), cmH <sub>2</sub> O	10 (8,10)	10 (8,12)	0.705
PSV, median (Q1, Q3), cmH <sub>2</sub> O	10 (8,12)	10 (8,12)	0.319
RR, median (Q1, Q3), bpm	18 (14, 22)	18 (15, 23)	0.952
pH, mean (SD)	7.43 (0.06)	7.43 (0.05)	0.483
PaO <sub>2</sub> /FiO <sub>2</sub> , median (Q1, Q3), mmHg	227 (192, 253)	211 (183, 245)	0.357
PaCO <sub>2</sub> , median (Q1, Q3), mmHg	44 (39, 50)	43 (40, 47)	0.714

Continuous data are reported as median(Q<sub>1</sub>, Q<sub>3</sub>) or mean (SD). Categorical data are report as No.(%). Abbreviations. BMI= Body Mass Index, ICU= Intensive Care Unit, SASPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment, RASS= Richmond Agitation Sedation Score, TRALI= transfusion-related acute lung injury, PEEP= Positive end-expiratory pressure, PSV=Pressure Support Ventilation, RR= Respiratory Rate, PAO<sub>2</sub>= partial pressure of oxygen, FiO<sub>2</sub>= inspired oxygen fraction; PaCO<sub>2</sub>= Partial pressure of carbon dioxide in the arterial blood,

<sup>a</sup> Test for difference Sigh vs No Sigh.

**e-Table 2. Sigh Non-Responders - Baseline characteristics.**

	Sigh (N=56)	No Sigh (N=46)	P Value <sup>a</sup>
Demographics			
Male, No.(%)	43 (77)	38 (83)	0.469
Age, mean (SD),y	64 (15)	65 (14)	0.861
Height, median (Q1, Q3), cm	170 (165, 178.5)	170 (162, 175)	0.499
Weight, median (Q1, Q3), Kg	79 (66, 90)	80 (70, 86)	0.984
BMI, median (Q1, Q3), Kg/m <sup>2</sup>	26.0 (22.9, 30.1)	26.4 (23.8-30.1)	0.503
Comorbidities, No.(%)			
Chronic cardiovascular disease	32 (57)	32 (70)	0.197
Chronic pulmonary disease	6 (11)	9 (20)	0.209
Diabetes	9 (16)	10 (22)	0.432
Chronic renal disease	6 (11)	11 (24)	0.075
Cancer	4 (7)	8 (17)	0.110
Number of comorbidities, No.(%)			
0	19 (34)	8 (18)	0.159
1	22 (40)	17 (38)	
2	10 (18)	11 (24)	
≥3	5 (9)	9 (20)	
Recent medical history			
In-hospital days, median (Q1, Q3)	5 (3, 7)	5.5 (3, 9)	0.427
ICU days, median (Q1, Q3)	3 (2, 5)	3 (2, 5)	0.881
Intubation days, median (Q1, Q3)	3 (2, 4.5)	3 (2, 5)	0.840
SAPS II, median (Q1, Q3)	42 (30, 53)	45 (33, 55)	0.561
SOFA, median (Q1, Q3)	8 (5, 10)	8 (5, 10)	0.661
RASS, No. (%)			
-2	26 (46)	25 (54)	0.706
-1	9 (16)	7 (15)	
0	21 (38)	14 (30)	

Diagnosis of sepsis, No. (%)			
Sepsis	20 (36)	14 (30)	0.147
Septic Shock	19 (18)	16 (35)	
Non septic	23 (41)	14 (30)	
Not Specified	3 (5)	2 (4)	
Etiology			
Pneumonia, No. (%)	35 (63)	28 (61)	0.866
Aspiration of gastric content, No. (%)	7 (13)	2 (4)	0.137
Vasculitis, No. (%)	0 (0)	1 (2)	1.000
Non-pulmonary sepsis, No. (%)	5 (9)	9 (20)	0.120
Trauma, No. (%)	4 (7)	2 (4)	0.137
Pancreatitis, No. (%)	1 (2)	1 (2)	0.799
Burns, No. (%)	1 (2)	0 (0)	0.549
TRALI, No. (%)	0 (0)	1 (2)	0.451
Others, No. (%)	4 (7)	4 (9)	1.000
Pulmonary infiltrates, No. (%)			
None	14 (25)	9 (20)	0.646
Unilateral	19 (34)	14 (30)	
Bilateral (ARDS diagnosis)	23 (41)	23 (50)	
PEEP, median (Q1, Q3), cmH <sub>2</sub> O	9.5 (8, 12)	9 (8,10)	0.498
PSV, median (Q1, Q3), cmH <sub>2</sub> O	10 (8,12)	10 (8,12)	0.181
RR, median (Q1, Q3), bpm	17 (14, 21)	19 (15, 22)	0.250
pH, mean (SD)	7.43 (0.05)	7.43 (0.07)	0.909
PaO <sub>2</sub> /FiO <sub>2</sub> , median (Q1, Q3), mmHg	211 (190, 257)	242 (198, 270)	0.187
PaCO <sub>2</sub> , median (Q1, Q3), mmHg	45 (38, 48)	44 (39, 48)	0.853

Continuous data are reported as median(Q<sub>1</sub>, Q<sub>3</sub>) or mean (SD). Categorical data are report as No.(%). Abbreviations. BMI= Body Mass Index, ICU= Intensive Care Unit, SASPS=Simplified Acute Physiology Score, SOFA=Sequential Organ Failure Assessment, RASS= Richmond Agitation Sedation Score, TRALI= transfusion-related acute lung injury, PEEP= Positive end-expiratory pressure, PSV=Pressure Support Ventilation, RR= Respiratory Rate, PAO<sub>2</sub>= partial pressure of oxygen, FiO<sub>2</sub>= inspired oxygen fraction; PaCO<sub>2</sub>= Partial pressure of carbon dioxide in the arterial blood,

<sup>a</sup> Test for difference Sigh vs No Sigh.

**e-Table 3. Analysis of time trends and differences of selected physiological variables (see e-Figure 1) between study groups.– GEE models**

Effect	F Value	P Value
<i>PEEP (cmH<sub>2</sub>O)<sup>a</sup></i>		
Time	7.72	<0.001
Group (Sigh vs. No Sigh)	0.01	0.943
Time* Group	1.44	0.198
<i>FiO<sub>2</sub></i>		
Time	1.55	0.163
Group (Sigh vs. No Sigh)	2.64	0.105
Time* Group	1.41	0.210
<i>PaO<sub>2</sub>/FiO<sub>2</sub> (mmHg)</i>		
Time	1.47	0.189
Group (Sigh vs. No Sigh)	5.35	0.022
Time* Group	1.75	0.110
<i>PaCO<sub>2</sub> (mmHg)</i>		
Time	3.79	0.001
Group (Sigh vs. No Sigh)	0.77	0.380
Time* Group	0.18	0.983
<i>Arterial pH</i>		
Time	0.39	0.887
Group (Sigh vs. No Sigh)	1.71	0.192
Time* Group	0.63	0.704
<i>RR (bpm)</i>		
Time	5.62	<0.001
Group (Sigh vs. No Sigh)	7.93	0.005
Time* Group	1.50	0.178
<i>Corrected MVe (l/min)<sup>a</sup></i>		
Time	1.13	0.3428
Group (Sigh vs. No Sigh)	4.80	0.0294
Time* Group	1.10	0.3614

<i>VT (ml/Kg PBW)<sup>a</sup></i>		
Time	2.46	0.025
Group (Sigh vs. No Sigh)	14.07	<0.001
Time* Group	2.07	0.058
<i>RASS<sup>b</sup></i>		
Time	4.31	<0.001
Group (Sigh vs. No Sigh)	1.36	0.245
Time* Group	0.70	0.652
<i>SOFA<sup>b</sup></i>		
Time	14.98	<0.001
Group (Sigh vs. No Sigh)	3.34	0.0689
Time* Group	1.14	0.341
<i>Sigh VT (ml/Kg PBW)<sup>a</sup></i>		
Time	1.96	0.077

Generalized Estimating Equation (GEE) models for repeated measures.

<sup>a</sup>Observations are truncated at extubation.

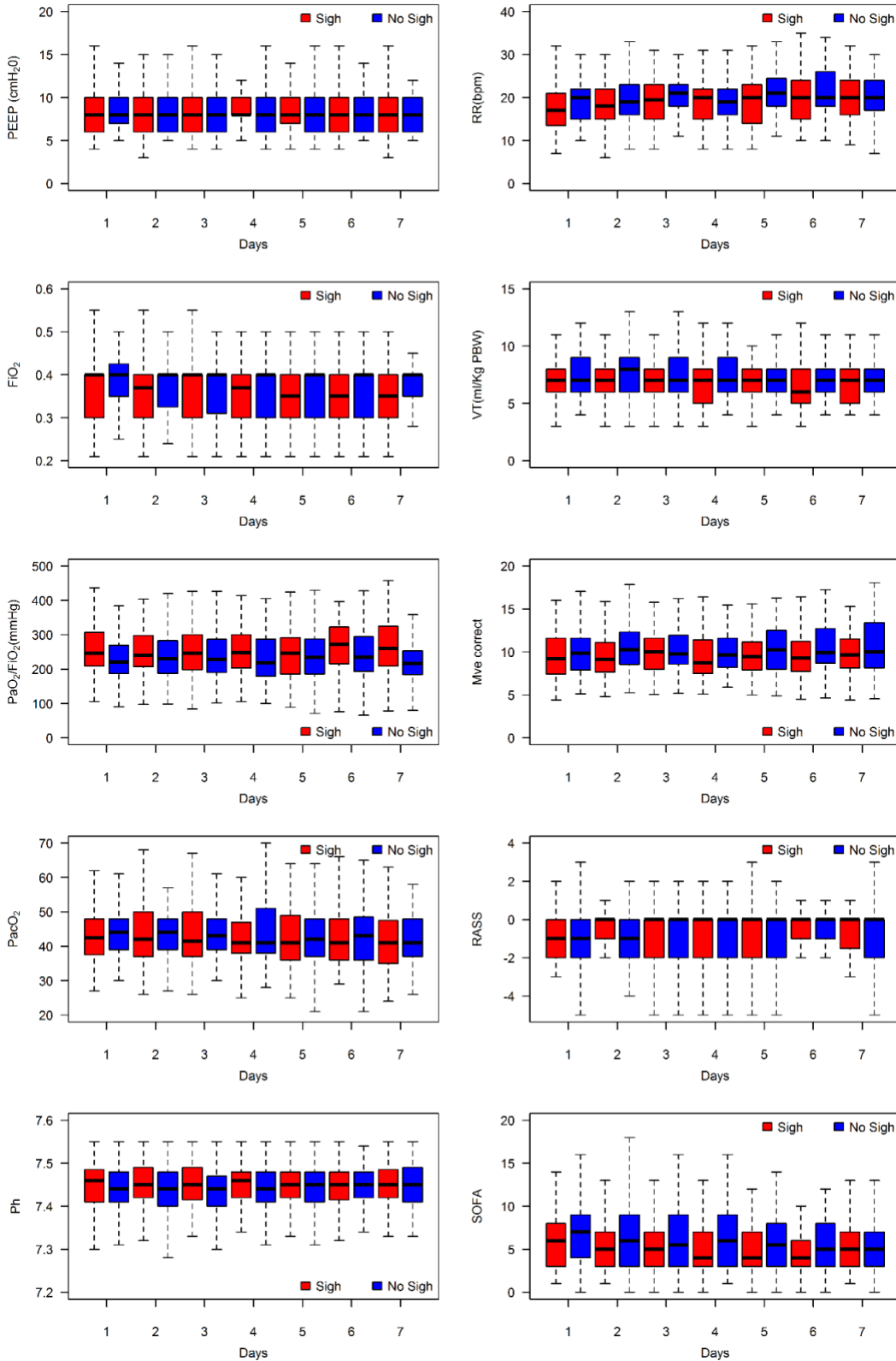
<sup>b</sup>Model with outcome normalizing transformation.



**e-Table 4. Number of patients included in the analyses presented in e-Figures 1 and 2 for each parameter in each group. Note that patients number decreases over time due to death or successful extubation.**

Days from randomization							
	1	2	3	4	5	6	7
PEEP (number of patients)							
Sigh	126	101	81	69	60	57	46
No Sigh	122	109	90	81	68	52	43
FiO <sub>2</sub>							
Sigh	128	126	107	93	88	72	64
No Sigh	128	123	114	104	94	82	70
PaO <sub>2</sub> /FiO <sub>2</sub>							
Sigh	128	125	106	91	86	71	63
No Sigh	128	122	113	103	92	79	67
PaCO <sub>2</sub>							
Sigh	128	125	112	93	87	71	64
No Sigh	128	123	115	105	95	79	69
pH							
Sigh	128	125	112	93	87	71	64
No Sigh	128	123	115	105	95	79	69
RR							
Sigh	128	123	106	92	86	72	64
No Sigh	128	121	113	103	95	82	70
VT							
Sigh	123	95	70	63	51	52	42
No Sigh	122	109	90	80	68	52	43
Corrected MVe							
Sigh	125	100	80	68	59	55	45
No Sigh	122	108	89	81	68	52	43
RASS							
Sigh	128	126	113	96	89	73	64
No Sigh	128	124	116	106	97	82	72
SOFA							
Sigh	128	126	113	95	89	73	64
No Sigh	128	123	116	105	96	82	72
Sigh VT							
Sigh	123	95	71	64	52	52	42

**e-Figure 1 – Physiological parameters in the 2 study arms over the first 7 days from randomization (for statistical analysis)**



**e-Figure 2. Tidal volume delivered by Sigh in the first 7 days from randomization**

