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Tolerability, Safety and Effectiveness of Sigh Introduction During Non-Invasive Mechanical Ventilation Cycles in Patients With Amyotrophic Lateral Sclerosis

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ABSTRACT

Background: Respiratory failure is the main cause of death in Amyotrophic lateral sclerosis (ALS), in which the physiological sigh reflex is impaired due to inspiratory muscle weakness. Aim of this study is to assess the tolerability, safety, and effectiveness of adding a sigh cycle to non-invasive mechanical ventilation (NIMV) settings in ALS patients.

Methods: In this randomized, blind-controlled proof-of concept study, 44 consecutive ALS patients with indication for NIMV were randomized to: Group I: NIMV with Sigh cycles; Group II: NIMV without Sigh. The primary outcome was the reduction in the Oxygen Desaturation Index (ODI); secondary outcomes included: Overnight Oximetry (OvOx), Arterial blood gas (ABG), and Visual Analog Scale (VAS; 0–10) scores to assess sleep quality, symptom intensity, mask interface, and NIMV tolerance. Assessments were conducted at baseline, after NIMV adaptation (T1) and at 1-month follow-up (T2).

Results: The Sigh cycle was safe and well tolerated. No significant group differences were observed at T1 or T2 in the primary outcome ODI (median ΔODI: Group A:−4.2; Group B:−4.6: $p = 0.54$), as well as in the OvOx parameters and pO_2 and pCO_2 ABG values. At T2, secondary analysis showed a significant difference in HCO_3^- in favor of the Sigh arm (ΔHCO_3^-: −1.60 vs. 1.35 mmol/L, $p = 0.042$). Exploratory Cox-regression models suggested a potential independent effect of SIGH on survival.

Conclusions: Sigh is safe, well tolerated in ALS patients. Although this study did not reach the primary outcome, we also cannot rule out that sigh doesn't benefit the patient.

1 | Introduction

Motor neuron diseases (MND) include a heterogeneous group of neurological disorders affecting the upper (UMN) and lower motor neurons (LMN), causing progressive spasticity and muscle weakness. Amyotrophic lateral sclerosis (ALS) represents the most aggressive and frequent form, leading to death within a mean time of 3–5 years from symptoms onset, most frequently due to respiratory failure [1]. In the absence of a cure, supportive therapies still represent the cornerstone

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of ALS management, including symptomatic treatment of respiratory failure. While previous studies have suggested that non-invasive mechanical ventilation (NIMV) may exert a beneficial effect on preserving quality of life and prolonging survival [2, 3], there are still many open questions regarding the most appropriate ventilation techniques and settings in this group of patients [4].

From a physiopathological perspective, muscle weakness, as observed in ALS and other neuromuscular disorders, can lead to respiratory muscle pump failure, characterized by decreased lung volumes and total lung capacity, resulting in increased work of breathing and the development of complications such as micro-atelectasis, de-recruitment, and worsening of the gas exchanges [2, 5–7]. Under physiological conditions, the reduced activation of the lung stretch receptors and hypoxia triggers the sigh reflex, leading to the onset of deep breaths, which play a critical role in controlling lung compliance by preventing the collapse of the alveoli, thus improving gas exchanges, restoring normoxia, and reducing the feeling of respiratory tension and discomfort [8, 9]. For these reasons, in acute respiratory distress syndrome (ARDS) and severe Chronic Obstructive Pulmonary Disease (COPD), the introduction of a Sigh in NIMV settings has been previously studied as a cyclic brief recruitment maneuver added to pressure support ventilation (PSV), showing effectiveness in improving lung elastance, enhancing the release of surfactant, decreasing regional ventilation heterogeneity, thus ameliorating gas exchanges and patients' outcomes [10–12]. Although the physiological sigh reflex cannot be effectively performed in ALS as a consequence of inspiratory muscle pump weakness and despite the growing recognition that lung recruitment strategies are essential in ALS respiratory management [7, 13], no studies to date evaluated the impact of the introduction of a Sigh in the NIMV settings in ALS patients. Hence, the aim of this randomized, blind-controlled proof-of concept study was to assess the tolerability, safety, and effectiveness of the Sigh in a group of patients with MND with NINV indication.

2 | Methods

2.1 | Study Design

This prospective monocentric, randomized, blind-controlled study was carried out in compliance with the World Medical Association Declaration of Helsinki's principles and was approved by the San Raffaele Hospital Ethics Committee (protocol ID: Sigh_01). Patients with amyotrophic lateral sclerosis (ALS) with indication to NIMV and meeting specific inclusion and exclusion criteria were consecutively selected from May 2018 to March 2022 (total duration: 45 months) (ClinicalTrials.gov ID: NCT04240925).

2.2 | Inclusion and Exclusion Criteria

During the period of study, patients with ALS with an indication to start NIMV adaptation according to current guidelines and to the principles of good clinical practice were consequently recruited, after written informed consent [14, 15]. All patients were admitted to the Department of Rehabilitation and Functional Recovery of the San Raffaele Hospital (OSR) and followed, in collaboration with the Respiratory Physiopathology Service, by a highly specialized multi-disciplinary team. Inclusion criteria: diagnosis of ALS according to El Escorial criteria [16]; current international ALS guidelines for the start of NIMV adaptation [2, 15]; valid informed consent. Exclusion criteria: previous episodes of pneumothorax; chronic heart failure; arrhythmias; presence of significant cognitive impairment of the patient; refusal by the patient.

2.3 | Randomization

At baseline, consecutive eligible patients were randomized to one of the two treatments in the study: Group A: adaptation to NIMV, including cycles of sigh breaths. The goal was to reach a sigh frequency of one sigh breath in every 200 ventilator-delivered breaths, with sigh pressure set to deliver 125% of the maximal inspiratory positive airways pressure. Frequency and pressure of the SIGH were increased depending on the patient's tolerance. Group B: adaptation to NIMV without SIGH cycle. Each patient was assigned to the treatment according to the randomization list. The randomization list was generated by a statistician independent of the study team using a dedicated program (www.randomization.com). This was a 1:1 randomization, with no stratification factors; the treatment allocation code was kept in a sealed, opaque envelope. NIMV treatment with and without SIGH were carried out by the treating team. The evaluations were carried out by an independent evaluator, kept blind to the patient's allocation.

2.4 | Adaptation to NIMV

After selection of the most tolerated and performing mask interface, patients were adapted to NIMV in PSV mode, with guaranteed target volume, with parameters tailored to the individual tolerability and effectiveness, according to respiratory function tests [2]. Target tidal volume was individualized based on respiratory function tests as well as anthropometric features (ideal body weight). Target tidal volumes of 6–8 mL/kg ideal body weight were typically recommended, as individually tolerated, according to standard procedures for neuromuscular patients [13, 17]. The Breas VIVO 50/55/45LS respirators were adopted; however, in three patients the Philiphs Respironics Trilogy 100 was used after T1 due to limitations in device availability within the patients' respective geographic areas. These devices allow the setting of a sigh in the NIMV parameters, which was added in patients randomized to Group A. Patients were considered adapted to NIMV when they were able to use it for at least 4 h/night for three consecutive days. Compliance to NIMV has been assessed using Vivo PC Software 3.3 (or later), which allows an objective recording of the number of hours of NIMV use per day.

2.5 | Assessments

At baseline, before the adaptation to NIMV (T0), all patients underwent an initial complete neurological and

pneumological examination, including demographics, site of onset, disease duration, diagnostic delay, Upper Motor Neuron (UMN) score (range: 0–16) [18, 19], Medical Research Council (MRC) sum score (range: 0–120) [20, 21], Edinburgh Cognitive and Behavioral ALS Screen (ECAS score) [22] and spirometry, to measure forced vital capacity (FVC) [2]. The evaluations of maximal inspiratory and expiratory pressures (MIP and MEP), sniff nasal inspiratory pressure (SNIP) and peak expiratory cough flow (PECF) were limited by the Sars-cov2 pandemic restrictions and the difficulty for the patient to effectively perform the requested manoeuvre; hence only available MIP and MEP data are reported. Disability was assessed with the revised ALS functional rating scale (ALSFRS-R) [21, 23, 24]; and the bulbar and respiratory sub-scores were separately derived. Disease progression rate was calculated by using the following formula: (48—ALSFRS-R score)/disease duration [21, 25]. Genetic testing was performed, as described, in all study patients, which tested negative for all major ALS-related genes [26]. Outcome measures included: Overnight Oximetry (OvOx), to measure Oxygen Desaturation Index (ODI, defined as the number of episodes per hour when blood oxygen saturation drops by at least 4% of basal value), basal SpO_2, time (in minutes) of $SpO_2 < 90\%$ (T90); Arterial blood gas analysis (ABG), to measure arterial pH, partial arterial pressure of oxygen (pO_2), and carbon dioxide (pCO_2); we also evaluated bicarbonate (HCO_3^-) and standard base excess (SBE), although not included in the original protocol, based on our recent findings [2]; Amyotrophic Lateral Sclerosis Assessment Questionnaire—5 items (ALSAQ-5), to assess health-related quality of life [27]; Pittsburgh Sleep Quality Index (PSQI) questionnaires [28] and two Visual Analog Scale (VAS; range: 0–10) to assess sleep quality and intensity of symptoms (dyspnoea) [29]. All assessments were conducted by an evaluator who was blinded to the patient randomization group, whereas a treating physician was responsible for NIMV treatment and parameters settings.

2.6 | Follow-Up

At discharge, after NIMV adaptation (T1), the outcome measures previously analyzed at T0 were repeated; in addition, two 0–10 VAS scales were administered in order to assess the degree of difficulty in adapting to the mask interface and tolerance to NIMV. The treating physician re-evaluated the patient's opportunity to continue treatment with SIGH in group A, in relation to the tolerability and NIMV effectiveness. Additionally, in order to explore medium-term effects, after 1 month from discharge (T2), each patient underwent a clinical re-evaluation, including a quantitative neurological examination, as described for T0, and repeated outcome measures, in accordance with patient availability. Although follow-up was partially limited for some patients by the Covid-19 pandemic restrictions, in all cases patients and family members had the possibility of being monitored with the help of telemedicine. After T2, patients were followed up in relation to the good clinical practice. A further exploratory outcome measure was the difference in survival (defined as death/placement of tracheotomy/need of NIMV for more than 20 h per day) between the two groups (last day follow-up: 31 September 2025). Survival time was defined as the month since baseline examination (T0).

2.7 | Statistical Analysis

The sample size was calculated with the GPower.3 4 power analysis software. The ODI Index at T1 was selected as the primary outcome [30]. An average ODI value of 15 (SD = 8) was estimated, based on previous reports of ALS patients previously adapted to NIMV in the OSR Neurorehabilitation ward [2]. It was determined that 44 patients (22 patients per treatment arm) would be required to achieve a power of 81% to detect a minimum clinically significant reduction of ODI values of 7 points (SD = 8; $\alpha = 0.05$ for a two-sided Student's *t*-test) at discharge (T1) compared with baseline. All statistical analyses were performed using the software Stata v 17 by an independent statistician, masked to the treatment allocation. We conducted a complete primary case analysis including all patients that were randomized according to their assigned treatment and with efficacy data at T1 and T2. For all the examined parameters mean, SD and median values were calculated. Group differences in changes from baseline in outcome measure values were evaluated using the Chi-square test for categorical variables and the Mann–Whitney *U*-test for continuous variables. Exploratory survival analysis was performed using Kaplan–Meier curves and the Mantel–Cox log-rank test, followed by a Cox multivariable proportional hazards model. Covariates were selected post hoc, chosen based on well-established prognostic variables, as described [31, 32]. For all analyses the level of significance was set at $p < 0.05$.

3 | Results

A total of 48 patients were screened for eligibility. Four patients did not meet the inclusion criteria and were therefore excluded. As a result, 44 patients were enrolled in the study, as planned, and randomly allocated to two groups (Figure 1). One patient from Group B was excluded due to a protocol deviation. At T1, one patient from Group B dropped out due to Sars-Cov pneumonia, subsequently leading to death. At T2, two patients from Group A and one patient from Group B dropped out because of death, while two patients, one from Group A and one from Group B, were lost at the follow-up examination due to Sars-Cov2 lock-down limitations. Consequently, the final sample size at T2 consisted of 19 patients in group A and 18 patients in group B.

Baseline features (T0) of Group A and Group B patients are summarized in Table 1. Notably, after randomization, no group differences were observed in demographic features, including disability (ALS-FRS-r), disease progression rate, and quality of life (measured with ALSAQ5). Similarly, concerning respiratory parameters, no significant differences were observed in FVC, ABG, oximetric parameters baseline values, even though their mean values were altered, coherently with a state of initial respiratory failure. VAS quality of sleep and respiration scales did not differ between groups (Table 1).

Following adaptation NIMV (T1), we observed an overall improvement in all respiratory outcome measures compared with baseline values (Table 2); however, no statistically significant differences between groups were observed, including the primary outcome ODI (median ΔODI: −4.2 in Group A vs. −4.5

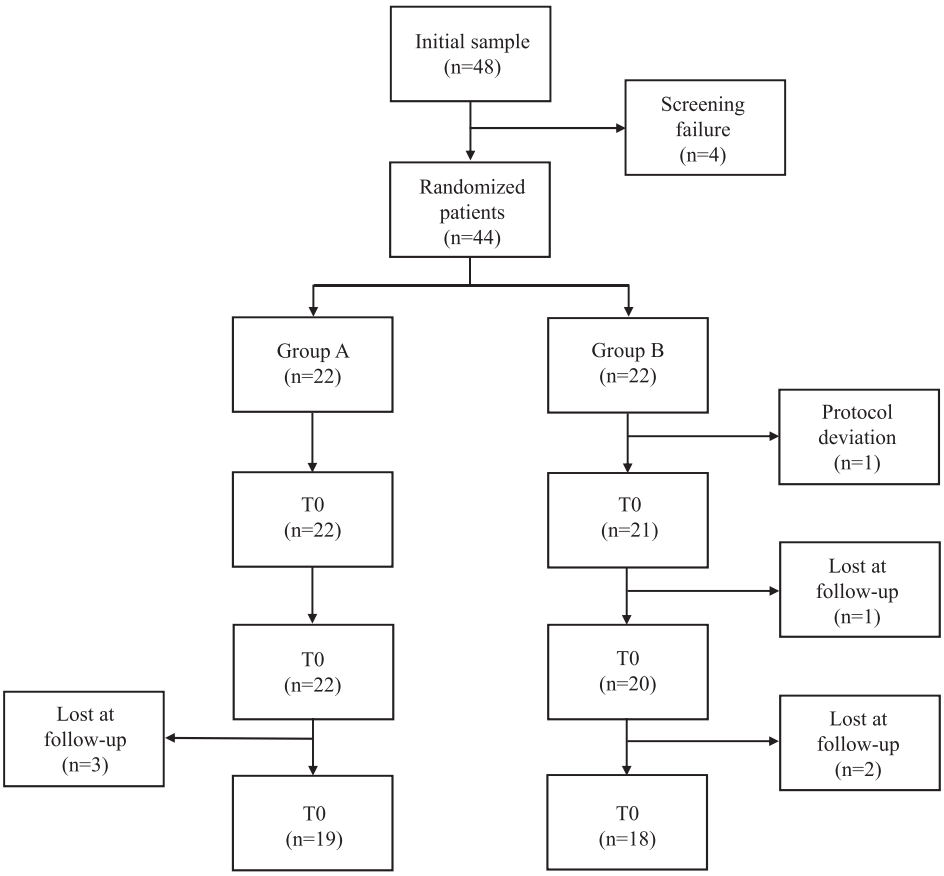

FIGURE 1 | Study population flowchart. T0, examination before the start of NIMV adaptation; T1, examination at the end of NIMV adaptation (discharge); T2, examination 1 month later the end of NIMV adaptation.

in Group B, $p = 0.67$) and the other overnight oximetry (OvOx) parameters. Similarly, at ABG we observed in both arms significant improvements in pCO_2, bicarbonate (HCO_3^-), and standard base excess (SBE) levels, again without intergroup differences. Changes in VAS scores for respiration and sleep between T0 and T1 did not differ between groups (Table 2). Per-protocol analysis confirmed these results (Table S1).

At one-month follow-up (T2), changes of OvOx from baseline values showed no statistically significant differences between groups (Table 3) (mean ΔODI: −4.6 in Group A vs. −5.0 in Group B, $p = 0813$) (Figure S1). Interestingly, the analysis of ABG parameters indicated a significant difference in changes from baseline in HCO_3^- in favor of patients allocated to the Sigh arm (mean ΔHCO_3^-: −1.60 mmol/L in Group A vs. 1.40 in Group B, $p = 0.028$). Per-protocol analysis confirmed these results, also showing a significant improvement in SBE values (mean ΔSBE: −1.0 mmol/L in Group A vs. 1.40 in Group B, $p = 0.037$) (Table S2). At T2, no significant differences between groups were observed in changes in the ALSFRS functional scale or the ALSAQ-5 and PSQI quality of life scales (Table S3), while NIMV settings and adherence were similar (Table S4). In subsequent clinical follow-up, one patient allocated to the active SIGH arm complained of aerophagy and flatulence: hence, the SIGH was turned off in the ventilator settings, even though there symptom persisted.

Exploratory assessment of the unadjusted effect on Sigh on survival showed a non-significant 7% decrease in the risk of death following NIMV adaptation (HR 0.93 [95% CI: 0.51–1.72], $p = 0.83$) (Figure 2A), while multivariable Cox's regression analysis (Table 4) identified the introduction of Sigh (HR 0.43 [95% CI: 0.21–0.89], $p = 0.022$) and diagnostic delay as independent prognostic factors of survival (Figure 2C). A per-protocol analysis (excluding two patients from Group B due to protocol deviations at follow-up) suggested a significant unadjusted treatment effect of Sigh on survival (HR 0.51 [95% CI: 0.26–1.00], $p = 0.049$), confirmed by Cox's multivariable analysis (HR 0.36 [95% CI: 0.17–0.76], $p = 0.007$) (Table 4; Figure 2B,D).

4 | Discussion

In this proof-of-principle randomized study, we investigated the tolerability, safety, and effectiveness of introducing a Sigh cycle in patients with ALS who had an indication for NIMV adaptation. Overall, the Sigh cycle was found to be safe and well tolerated, supporting its feasibility as a NIMV setting option in this patient population. Since the pre-specified primary efficacy outcome was not achieved, the results of the trial cannot provide sufficient evidence that "sigh" provides a benefit. However, analysis of secondary outcome measures at follow-up suggested a potential benefit in terms of gas exchange and survival among patients in whom the Sigh cycle was incorporated into the NIMV settings, hence, we also cannot rule out that the sigh doesn't benefit the patient.

Although one of the main complications of restrictive respiratory failure associated with neuromuscular weakness in

TABLE 1 | Baseline descriptive statistics of all patients included in the study (ITT population).

			Group A (Sigh ON)		Group B (Sigh OFF)		
		Total	***N***	**%**	***N***	**%**	**|StD|**
Clinical parameters	Sex: Males	44	11	(50%)	15	(68.2%)	0.304
	Bulbar onset	44	3	(13.7%)	7	(31.8%)	0.382
	MIE	44	17	(77.3%)	14	(63.6%)	0.253
	Nutr failure	44	10	(45.5%)	11	(50.0%)	0.074

			Group A (Sigh ON)			Group B (Sigh OFF)			
		Total	***N***	**Mean**	**SD**	***N***	**Mean**	**SD**	**|StD|**
Clinical parameters	Age	44	22	66.95	12.42	22	64.36	15.64	0.183
	BMI	44	22	22.49	3.37	22	22.36	4.08	0.035
	Diagnostic delay	44	22	11.14	11.03	22	19.59	28.98	0.386
	Disease duration	44	22	23.31	20.48	22	38.86	48.45	0.418
	ALSFRS-R	44	22	28.18	7.34	22	28.95	6.05	0.115
	ALSFRS-R (Resp)	44	22	9.41	2.15	22	10.14	1.75	0.372
Clinical Scales	ALSFRS-R (Bulbar)	44	22	8.82	3.11	22	8.68	2.85	0.047
	DPR	44	22	1.45	1.12	21	0.97	0.75	0.501
	ECASS (total)	36	18	96.61	26.86	18	87.22	23.28	0.374
	ECASS (specific domains)	36	18	71.72	21.33	18	64.78	18.14	0.351
	ALSAQ5	44	22	10.68	4.16	22	10.00	5.18	0.145
	FVC (%)	37	18	55.44	18.41	19	54.13	20.61	0.067
	MIP (%)	23	12	39.1	17.9	11	29.6	13.8	0.586
	MEP (%)	23	12	33.9	27.0	11	28.4	20.9	0.225
Overnight Oximetry	ODI	44	22	12.36	13.90	22	12.53	12.94	0.013
	Basal SpO2	44	22	91.20	1.68	22	90.70	3.30	0.192
	T90	44	22	114.5	125.7	22	105.3	124.3	0.074
ABG	pO_2	43	21	79.74	8.53	22	80.06	10.96	0.033
	pCO_2	42	20	44.61	7.54	22	43.10	8.43	0.188
	pH	43	21	7.41	0.04	22	7.41	0.03	0.456
	HCO_3	41	20	27.66	3.05	21	26.83	4.20	0.224
	SpO_2	43	21	93.16	10.90	22	94.78	3.66	0.201
	SBE	41	20	2.70	2.22	21	1.95	2.87	0.292
VAS Scales	VAS Sleep	44	22	6.14	2.32	22	6.73	2.37	0.251
	VAS Resp.	44	22	2.27	2.07	22	1.41	2.72	0.356

Abbreviations: ABG, arterial blood gas analysis; BMI, body mass index (kg/m^2); DPR, disease progression rate; FVC, forced vital capacity; gastrostomy acceptance, Group A: 5/10 (50%), Group B: 8/11 (72.7%); HCO_3, bicarbonates (mmol/L); ITT, intention to treat; MEP, maximal expiratory pressure; MIE: mechanical insufflation-exsufflation (cought assis) use (T0-T2); MIP, maximal inspiratory pressure; *N*, sample size; Nutr Fail, nutritional failure; ODI, oxygen desaturation index; $PaCO_2$, partial pressure of a carbon dioxide (mmHg); PaO_2, partial pressure of oxygen (mmHg); $SatO_2$ or SpO_2, saturation of oxygen (%); SBE, standard base excess (mmol/L); SD, standard deviation; StD, standardized difference; T90, time in minutes of SpO_2 under 90%; VAS, Visual Analogue Scale.

ALS is the reduced alveolar recruitment—leading to their exclusion from gas exchange and the potential development of microatelectasis—and despite the positive outcomes observed with Sigh in other conditions such as COPD and ARDS, to date no studies have investigated its usefulness in ALS [5–7, 13] According to our results, however, Sigh confirmed a favorable tolerability profile in this patient population, in line with other conditions [10–12, 33]. Indeed, during the adaptation period, mask fit and NIMV tolerability were comparable between patients with and without the Sigh cycle. At follow-up,

TABLE 2 | Comparison of respiratory parameter changes between groups from baseline (T0) to end of NIMV adaptation (T1) in the ITT population.

			Group A (Sigh ON)			Group B (Sigh OFF)			
		Total	*N*	Median	IQR	*N*	Median	IQR	*p*
OvOx parameters	ΔODI	41	22	−4.2	−9.0/−0.5	19	−4.6	−12.70/−0.80	0.539
	Δ Basal SpO_2	41	22	1.75	−0.1/3	19	2	1/3.6	0.187
	ΔT90	41	22	−53.6	−161.7/0.1–166.1/4.3	19	−47.4	−151/−11.7	0.794
Arterial blood gas analysis	ΔpCO_2	38	20	−3.45	−6.7/0.45	18	−0.3	−4.3/3.3	0.430
	ΔpH	39	21	0.00	0–00/0.023	18	0.01	−0.03/0.03	0.461
	ΔHCO_3	37	20	−1.40	−2.85/0.35	17	−1	−2/0.5	0.637
	Δ$SatO_2$	38	21	0.00	−0.70/1.60	17	0.20	−1.1/1.3	0.918
	ΔBE	35	18	−0.65	−2.25/0.725	17	−0.8	−2.8/0	0.680
QoL scales	ΔPaO_2	38	20	−2.65	−4.5/9.55	18	2	−7.60./8.9	0.654
	ΔVAS Sleep	43	22	0.00	0.00/2.00	21	0.00	−1.00/1.00	0.358
	ΔVAS Respiration	43	22	−1.00	−2.25/2.25	21	0.00	−1/1	0.396
	VAS Mask	43	22	3.0	1.0/6.0	21	5.0	1.0/6.0	0.711
	VAS NIMV	43	22	2.0	0.0/3.5	21	3.0	0.0/6.0	0.400

Abbreviations: ABG, arterial blood gas analysis; BMI, body mass index (kg/m²); HCO3, bicarbonates (mmol/L); *N*, sample size; ODI, oxygen desaturation index; $PaCO_2$, partial pressure of a carbon dioxide (mmHg); PaO_2, partial pressure of oxygen (mmHg); $SatO_2$ or SpO_2, saturation of oxygen (%); SBE, standard base excess (mmol/L); SD, standard deviation; T90, time in minutes of SpO_2 under 90%; VAS, Visual Analogue Scale.

TABLE 3 | Comparison of respiratory parameter changes between groups from baseline (T0) to 1-month follow-up (T2) in the ITT population.

			Group A (Sigh ON)			Group B (Sigh OFF)			
		Toal	*N*	Median	IQR	*N*	Median	IQR	*p*
OvOx parameters	ΔODI	33	17	−4.6	−8.5/−0.3	16	−5.7	−14.6/−2.55	0.471
	ΔSpO_2 basal	33	17	1.80	0.8/3.1	16	1.7	0.45/3.1	0.66
	Δ%T < 90%	33	17	−62.4	−163.4/−7.8	15	−40.9	−117.6/5.6	0.610
Arterial blood gas analysis	ΔpCO_2	32	16	−3.05	−6.82/0.85	16	−2.55	−8.42/1.85	0.149
	ΔpH	33	17	0.01	−0.02/0.04	16	−0.005	−0.005/0.02	0.9423
	ΔHCO_3	32	16	−1.60	−3.15/−0.30	16	1.35	−2.3/2.4	**0.042**
	Δ$SatO_2$	32	17	−0.10	−0.4/1.5	15	0.40	−0.50/2	0.821
	ΔBE	29	15	−1	−2.3/0.3	14	1.25	−1.2/3	**0.055**[*]
	ΔPaO_2	33	17	2.9	−2.5/9.9	16	75.15	−3/19.15	0.773

Note: Statistically significant results are shown in bold.
Abbreviations: ABG, arterial blood gas analysis; BMI, Body Mass Index (kg/m²); HCO_3, bicarbonates (mmol/L); *N*, sample size; ODI, Oxygen Desaturation Index; $PaCO_2$, partial pressure of a carbon dioxide (mm Hg); PaO_2, partial pressure of oxygen (mm Hg); $SatO_2$ or SpO_2, saturation of oxygen (%); SBE, standard base excess (mmol/L); SD, standard deviation; T90, time in minutes of SpO_2 under 90%; VAS, Visual Analogue Scale.
[*]Significant difference in the per-protocol analysis (Table S2).

one patient randomized to Group A required discontinuation of the Sigh due to aerophagia—a common side effect associated with NIMV—which persisted even after the Sigh cycle was turned off [34].

At T1, after NIMV adaptation, both groups experienced an improvement of the respiratory measurements, confirming the beneficial effect of NIMV [35–40]. However, no significant group differences in respiratory outcome measures were observed, including the primary outcome measure ODI. Sigh has been primarily studied in hypoxemic patients with ARDS, where two studies demonstrated an improvement in oxygenation, likely due to enhanced alveolar recruitment [10, 11], while in one study the application of sigh in patients with COPD has shown

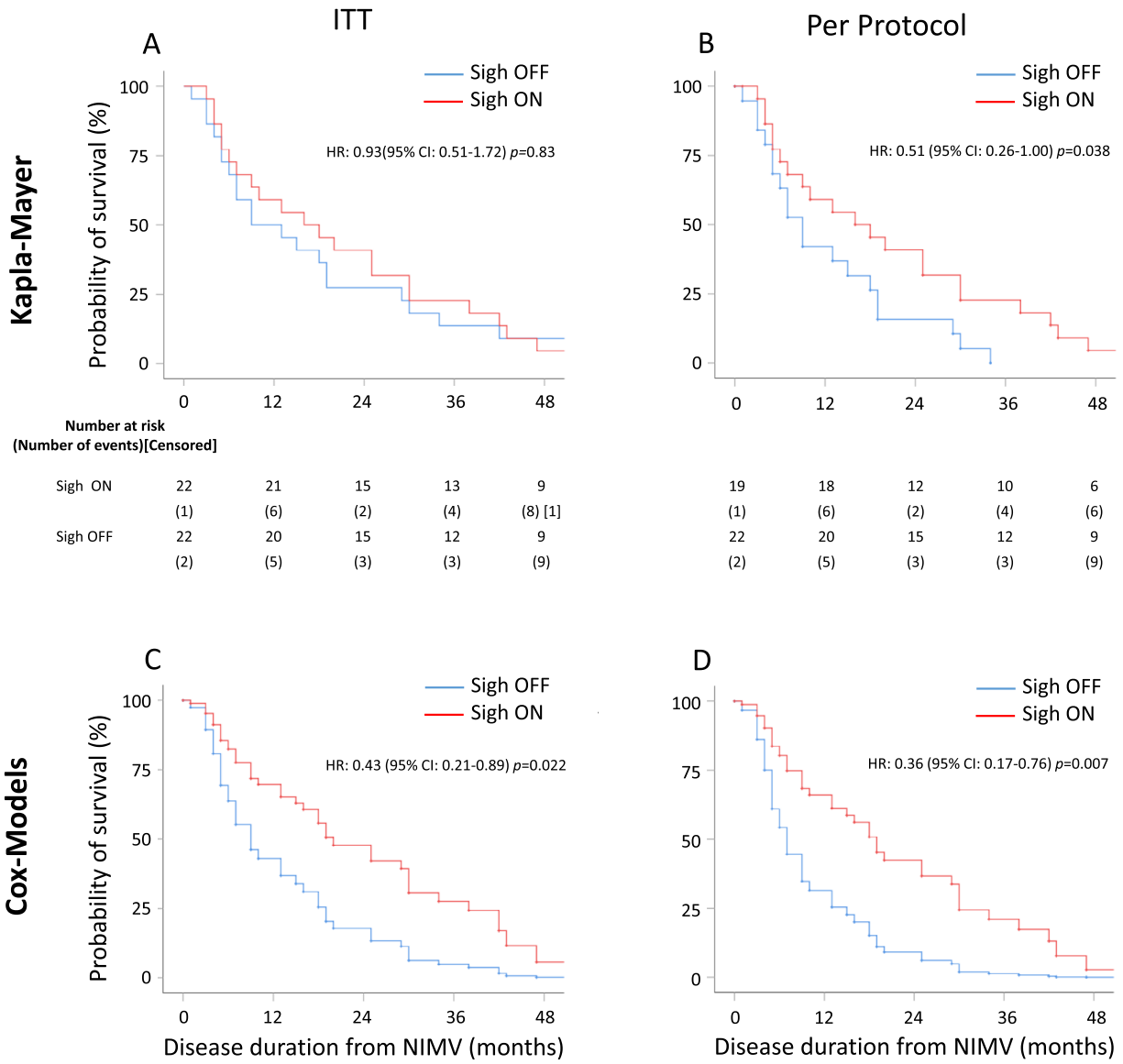

FIGURE 2 | Survival analysis. (A) Kaplan–Meier curves of study patients (A: ITT population; B: Per-protocol analysis). (C and D) Cox regression models for the ITT (C) and per-protocol analysis (D): Variables in the model: Age, El-Escorial Criteria (ALS Definite); disease progression rate; Site of onset (Bulbar vs. Spinal; diagnostic delay). ITT, intention to treat.

TABLE 4 | Cox regression survival models.

		Intention to treat		Per protocol	
Variables		**HR (95% CI)**	***p***	**HR (95% CI)**	***p***
SIGH	OFF	1		1	
	ON	0.428 (0.206–0.886)	**0.022**	0.359 (0.171–0.755)	**0.007**
Age		1.028 (0.999–1.059)	0.058	1.021 (0.989–1.054)	0.210
Escorial criteria	Definite-ALS	0.117 (0.478–2.607)	0.798	0.905 (0.373–2.196)	0.825
Disease progression rate		1.406 (0.929–2.129)	0.107	1.585 (1.011–2.486)	**0.045**
Site of onset	Spinal	1		1	
	Bulbar	1.755 (0.788–3.912)	0.169	1.452 (0.642–3.284)	0.370
Diagnostic delay		0.973 (0.951–0.996)	**0.021**	1.000 (0.959–1.042)	0.998

Note: HR, hazard ratio; Survival time was defined as month since baseline examination (T0). Statistically significant results are shown in bold.

that sigh combined with NIMV was more effective in reducing CO_2 levels than NIMV alone. This effect may be attributed to decreased ventilation heterogeneity or improved regional lung mechanics, thereby promoting gas exchange [8, 33]. In this study, no statistically significant differences in ABG values were observed, although improvements in pCO_2 and pO_2 appeared in favor of the Sigh group. However, the Sigh has been previously investigated primarily in settings of more acute disease and typically implemented with higher intensities and levels [10–12, 33, 41], which may account for the absence of significant short-term major ABG changes in the present study.

At the one-month follow-up, outcome analysis confirmed the absence of any significant between-group differences in changes from baseline in OvOx parameters, including ODI, as well as pO_2 and pCO_2 ABG levels. This finding suggests that, under the conditions of our study, the application of Sigh did not translate into measurable improvements in oxygenation or ventilation when compared with the control group. However, in Sigh recipients, we observed a significant improvement from baseline of both HCO_3^- and BE levels, which may be explained by a medium-term metabolic beneficial effect of Sigh on gas exchange and acid–base balance, potentially reflecting a more efficient gas exchange over time. One possible explanation is that the recruitment effect of Sigh could prevent microatelectasias, enhance alveolar ventilation and reduce subtle ventilation–perfusion mismatches [7]. Although these changes did not translate into significant differences in primary ABG parameters, they may represent an early metabolic adaptive response with potential clinical longer-term relevance [35]. This study was not specifically designed or powered to evaluate survival outcomes; however, the hypothesis is supported by the results of Cox multivariable regression models and by the per-protocol Kaplan–Meier analysis, both indicating longer survival in ALS patients receiving Sigh as part of the NIMV parameter setting compared with those who did not. Larger and more robustly designed studies will be required to confirm or refute the preliminary observations reported here. Additionally, no significant effects on quality of life measures were detected, despite previous reports suggesting that Sigh may participate in the regulation of emotions such as anxiety, by reducing the feeling of respiratory tension and discomfort in ventilated patients [9].

To our knowledge, this is the first study to evaluate the efficacy, safety, and tolerability of Sigh in patients with ALS. Nevertheless, several limitations should be acknowledged. The most important limitation is the small sample size, which limits the statistical power and precludes definitive conclusions. Furthermore, the study was partially conducted during the COVID-19 pandemic, which resulted in loss to follow-up for some participants, increased missing data rates, hence further reducing the sample size, limiting the statistical power of the study and potentially introducing bias. Another limitation is the absence of advanced respiratory assessments, such as transcutaneous capnography or polysomnography, as well as the lack of consideration for all variables related to the multi-disciplinary care of the advanced stages of the disease, such as the complex management of nutritional failure, including gastrostomy positioning, as well as cough assist use, that may influence outcomes, even though the specific contribution of each individual intervention on survival remains to be clearly defined [42]. Additionally, one additional major limitation is blinding, which was limited by the intrinsic features of the study design. To address this issue, all assessments were conducted by an independent evaluator who remained blinded to treatment allocation. Additionally, patients were not informed of treatment allocation and the ventilator's "Sigh" setting is not easily accessible, as it appears only in a secondary window of the embedded software. However, we acknowledge that patient unblinding could still occur and that the degree of blinding was not formally measured, which is a major limitation. Therefore, the risk of bias associated with unmasking cannot be excluded. Regarding the possibility of a sham setting, implementing a true sham NIMV intervention would be challenging. Nevertheless, future studies might consider randomization to different incremental "doses" (in terms of frequency and pressure values) of the sigh setting, thereby introducing additional treatment groups. This approach could partially address the issue inherent to mechanical ventilation interventions. In addition, although NIMV adherence and settings were similar between groups at T2, no systematic quantitative adherence by-protocol monitoring was available beyond this point, as patients were instead managed according to best clinical practice. Therefore, no definitive conclusions regarding the long-term effects of sight can be drawn from this study, underscoring the need for future investigations that are rigorously designed to control for potential confounding factors. Despite these limitations, NIMV adaptation was performed by a specialized team of neurologists and pulmonologists with extensive experience in ALS management, and all interventions were individualized to meet patient-specific needs and this trial provides preliminary evidence that can inform the design of future studies, including the appropriate selection of primary outcome measures. Indeed, the choice of ODI as the primary outcome was based on its prior use as a primary and secondary endpoint in NIV trials involving ALS and non-neuromuscular populations, as well as its role as a secondary outcome in studies of neuromuscular disorders [30]. However, respiratory failure in ALS is primarily driven by hypoventilation rather than obstructive or central apnoea, and patients may have significant REM hypoventilation without an elevated ODI [13], which may explain why a difference was not detected at T1 or T2. Hence, we acknowledge that measures of hypoventilation may be considered more appropriate primary outcomes for future NIV trials than oxygen desaturation indices alone, in both ALS and other neuromuscular diseases [13, 43]. As this was the first trial to investigate sigh breaths in neuromuscular patients outside the acute care setting, these challenges may inform the design of future studies.

In conclusion, this proof-of-concept study indicates that incorporating Sigh into NIMV cycles is safe and well tolerated in patients with ALS. The results of the trial cannot provide sufficient evidence that "sigh" provides a benefit, but also cannot rule out that it doesn't benefit the patient, hence a larger trial is needed that may best focus on either survival or the arterial blood gas analyses.

Author Contributions

Andrea Tettamanti: investigation, project administration, resources, writing – review and editing, supervision. **Nilo Riva:**

conceptualization, data curation, investigation, supervision, funding acquisition, visualization, project administration, resources, writing – review and editing, validation, methodology. **Paride Schito:** data curation, investigation, supervision, visualization, writing – original draft, methodology. **Gianluca Durante:** data curation, investigation, visualization, writing – original draft. **Mauro Comola:** conceptualization, supervision, resources, writing – review and editing, methodology. **Elisa Riboldi:** resources, supervision, writing – review and editing, investigation, project administration. **George Cremona:** conceptualization, data curation, funding acquisition, supervision, resources, writing – review and editing, validation, investigation, methodology. **Massimo Filippi:** funding acquisition, supervision, resources, writing – review and editing. **Teuta Domi:** investigation, writing – review and editing, validation. **Angelo Quattrini:** funding acquisition, investigation, project administration, resources, writing – review and editing, supervision. **Federica Agosta:** resources, writing – review and editing, supervision. **Laura Pozzi:** investigation, validation, writing – review and editing. **Ottavia Eleonora Ferraro:** conceptualization, data curation, formal analysis, writing – review and editing, software, methodology. **Tommaso Russo:** investigation, data curation, visualization, writing – review and editing.

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Ethics Statement

This study was conducted in compliance with the Declaration of Helsinki and approved by the Ethics Committee of San Raffaele Hospital (protocol ID Sigh_01). Written informed consent was obtained from each enrolled participant (ClinicalTrials.gov ID: NCT04240925).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Comparison of respiratory parameter changes between groups from baseline (T0) to end of NIMV adaptation (T1): per protocol population. **Table S2:** Comparison of respiratory parameter changes between groups from baseline (T0) to 1-month follow-up (T2): per-protocol population. **Table S3:** Comparison analysis of the differences from T2 to T0 measurements of the clinical and quality of life scales between groups. **Table S4:** Ventilator settings at T1 and adherence at T2. **Figure S1:** Spaghetti plot for pCO_2 and ODI, ITT population.