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RESEARCH ARTICLE

Arterial blood gas analysis: base excess and carbonate are predictive of noninvasive ventilation adaptation and survival in amyotrophic lateral sclerosis

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Abstract

Objective: To investigate the role of arterial blood gas (ABG) analysis parameters (blood carbon dioxide, pCO₂; oxygen, pO₂; carbonate, HCO₃⁻; standard base excess, SBE) in monitoring respiratory function and ventilation compliance after noninvasive mechanical ventilation (NIV) adaptation, predicting survival in ALS patients. **Methods:** We selected the first ABG performed after NIV start in ALS patients followed from 2000 to 2015 in Turin ALS Center. Correlations between ABG parameters and survival were calculated. Risk for death/tracheostomy was computed at modifying ABG parameters by using Cox regression models, adjusted for the main prognostic factors. Kaplan–Meier curves were then performed and compared. **Results:** A total of 186 post-NIV ABGs were included. HCO₃⁻ and SBE showed a significant correlation with survival after NIV (respectively, $R = -0.183$, $p = 0.018$ and $R = -0.200$, $p = 0.010$). Risk for death/tracheostomy after NIV was significantly higher at increasing HCO₃⁻ and SBE blood levels, especially when HCO₃⁻ was >29 mmol/L and SBE >4 mmol/L (respectively, HR 1.466, 95% CI 1.068–2.011, $p = 0.018$ and HR = 1.411, 95% CI 1.030–1.32, $p = 0.032$). Survival in NIV was higher in patients with HCO₃⁻ < 29.0 mmol/L and SBE < 4.0 mmol/L. **Conclusions:** HCO₃⁻ and SBE blood levels are markers of ventilation compliance, tolerance and efficacy, being able to predict survival after NIV start in ALS.

Keywords: Amyotrophic lateral sclerosis, noninvasive mechanical ventilation, arterial blood gas analysis, carbonate, standard base excess

Introduction

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder affecting motor neurons. A critical aspect of the disease is respiratory failure due to respiratory muscles weakness that occurs during the course of the disease.

Noninvasive mechanical ventilation (NIV) is recognized as the treatment of choice for impending symptoms and signs of respiratory failure, improving patients’ quality of life and survival (1). Patients’ compliance to NIV and adequate ventilator settings are crucial for improving long-term NIV efficacy (2,3).

In this study, we aimed at investigating the role of arterial blood gas (ABG) parameters, such as blood carbon dioxide (pCO₂), oxygen (pO₂), carbonate (HCO₃⁻), and standard base excess (SBE), in monitoring respiratory function after NIV adaptation and predicting patients’ survival.

Materials and methods

Data collection

All clinical records of ALS patients included in the Piemonte and Valle d’Aosta ALS Registry

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(PARALS) and diagnosed from 2000 to 2015 in Turin ALS Center were checked. We collected a dataset including the ABGs performed after NIV start. For patients who performed more than one post-NIV ABG, we selected the first one for our analysis. ABGs were performed in the morning through radial arterial puncture by a trained nurse or pulmonologist and immediately analyzed using blood gas analyzer, routinely calibrated, as appropriate.

Patients with severe medical conditions or with signs of uncompensated acidosis/alkalosis (ABG pH <7.35 and >7.45) were excluded from the analysis. For each patient, we collected age at onset, sex, site of onset, date of diagnosis, date of death/tracheostomy, date of ABG, and date of ALSFRS-r scale. Survival was assessed from the date of ABG to death/tracheostomy or censoring date (31st December 2018). The disease progression rate (Δ ALSFRS) was computed as the ratio between the difference 48—ALSFRS-r at the time of ABG and the time interval in months between onset and the day of ABG. Bulbar involvement at time of ABG was derived from the scores in the first three ALSFRS-r scale items. It was classified as absent if all three items had a score equal to 4, moderate if at least one of them had a score equal to 3 or 2, severe if at least one of them had a score equal to 1 or 0.

We considered as NIV-treated all the patients who were prescribed NIV and used it for at least 1 day (intention-to-treat analysis) (4). NIV prescription was always done by an expert pulmonologist, who followed the most updated clinical practice guidelines (5–7).

Statistical analysis

Differences of discrete and continuous variables were analyzed using the χ^2 test and Student's *t* test or Wilcoxon rank-sum and Mann–Whitney *U* tests, respectively. A *p* value <0.05 was considered significant. Correlations between ABG parameters (pCO₂, pO₂, HCO₃[−], SBE) and disease duration from date of ABG were calculated using the non-parametric two-tailed Spearman's rank correlation test. In order to check a significant increase of risk of death/tracheostomy, we assessed the association between ABG values and survival, by using Cox proportional hazards models, adjusted for sex, age at onset, bulbar involvement at time of ABG and Δ ALSFRS. Kaplan–Meier curves were then performed and compared with log rank test. Data were analyzed using IBM SPSS Statistics for Windows, Version 26.0. IBM Corp. Released 2019.

Standard protocol approvals, registrations, and patient consents. The study design was approved by the Ethical Committee of the Azienda

Ospedaliero-Universitaria Città della Salute of Turin (Prot. N. 0036344).

Results

A total of 186 post-NIV ABGs were included in our analysis. Descriptive statistics of patients are shown in Table 1. Median time interval between NIV start and ABG was 32.0 days (IQR 14.0–92.3).

Among ABG parameters, HCO₃[−], SBE, and pH showed a significant correlation with survival on NIV (respectively $R = -0.183$, $p = 0.018$ for HCO₃[−]; $R = -0.200$, $p = 0.010$ for SBE; for pH $R = -0.175$, $p = 0.024$) as shown in Table 2.

Risk for death/tracheostomy in NIV was significantly higher at increasing HCO₃[−] and SBE blood levels (respectively, for HCO₃[−] HR 1.055, 95% CI 1.017–1.095, $p = 0.004$; for SBE HR = 1.060, 95% CI 1.020–1.101, $p = 0.003$, Table 3). In particular when HCO₃[−] levels were higher than 29 mmol/L and SBE exceeded 4 mmol/L a significant increase for death/tracheostomy was found (for HCO₃[−] HR 1.466, 95% CI 1.068–2.011, $p = 0.018$; for SBE HR = 1.411, 95% CI 1.030–1.32, $p = 0.032$, Table 4).

Table 1. Descriptive statistics ($n = 186$ patients).

Epidemiological characteristics	<i>N</i> (%)
Sex	77 (41.4%) F 109 (58.6%) M
Site of onset (bulbar vs. spinal)	54 (29.0%) bulbar 132 (71.0%) spinal
Bulbar involvement at time of ABG	131 (70.4%) Median (IQR)
Age at onset (years)	65.0 (69.0–71.0)
Overall survival (years)	2.52 (1.76–3.95)
Survival after NIV (years)	0.73 (0.33–1.51)
Time onset–NIV (years)	1.59 (0.92–2.86)
Time NIV–ABG (days)	32.0 (14.0–92.3)
Δ ALSFRS	0.59 (0.40–0.89)
pCO ₂	45.0 (41.0–50.0)
pO ₂	75.8 (68.7–83.0)
HCO ₃ [−]	28.2 (25.7–31.4)
SBE	3.71 (1.45–7.09)
pH	7.42 (7.40–7.44)

ABG: arterial blood gas analysis; NIV: noninvasive ventilation; SBE: standard base excess.

Table 2. Correlations between ABG parameters and survival from date of post-NIV ABG.

ABG parameter	<i>R</i>	* <i>p</i> Value
pCO ₂	−0.093	0.231
pO ₂	0.036	0.645
pH	−0.175	0.024
HCO ₃ [−]	−0.183	0.018
SBE	−0.200	0.010

SBE: standard base excess.

**p*-value < 0.05 was considered significant and written in bold.

Table 3. Risk for death/tracheostomy from date of post-NIV ABG.

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	* <i>p</i> Value	HR (95% CI)	* <i>p</i> Value
Age at onset	1.020 (1.000–1.040)	0.047	1.007 (0.986–1.028)	0.516
Bulbar involvement	1.256 (0.884–1.785)	0.204	1.128 (0.782–1.628)	0.520
Sex	0.976 (0.709–1.342)	0.881	1.132 (0.813–1.576)	0.463
ΔALSFRS	1.004 (1.002–1.006)	<0.001	1.004 (1.003–1.006)	<0.001
pCO ₂	1.019 (0.998–1.042)	0.080	1.064 (0.841–1.346)	0.604
pO ₂	0.992 (0.976–1.009)	0.366	1.001 (0.982–1.019)	0.950
HCO ₃ ⁻	1.053 (1.015–1.092)	0.006	1.055 (1.017–1.095)	0.004
SBE	1.057 (1.018–1.099)	0.004	1.060 (1.020–1.101)	0.003

Cox regression univariate and multivariate analysis adjusted for the main prognostic factors in ALS. SBE: standard base excess.
 **p*-value < 0.05 was considered significant and written in bold.

Table 4. Risk for death/tracheostomy from date of post-NIV ABG.

ABG parameter	Univariate analysis		Multivariate analysis	
	HR (95% CI)	* <i>p</i> Value	HR (95% CI)	* <i>p</i> Value
Age at onset	1.020 (1.000–1.040)	0.047	1.009 (0.989–1.029)	0.396
Bulbar involvement	1.256 (0.884–1.785)	0.204	1.179 (0.823–1.689)	0.368
Sex	0.976 (0.709–1.342)	0.881	1.093 (0.781–1.530)	0.604
ΔALSFRS	1.004 (1.002–1.006)	<0.001	1.004 (1.002–1.006)	<0.001
pCO ₂	1.019 (0.998–1.042)	0.080	1.010 (0.982–1.039)	0.475
pO ₂	0.992 (0.976–1.009)	0.366	1.003 (0.985–1.021)	0.787
HCO ₃ ⁻ >29.0 mmol/L	1.490 (1.087–2.041)	0.013	1.466 (1.068–2.011)	0.018
SBE >4.0 mmol/L	1.433 (1.047–1.960)	0.025	1.411 (1.030–1.932)	0.032

Cox regression univariate analysis and multivariate analysis adjusted for the main prognostic factors in ALS, considering cutoffs for HCO₃⁻ and SBE (cut-off corresponding to the median value of ABG parameter among patients).
 **p* value <0.05 was considered significant and written in bold.

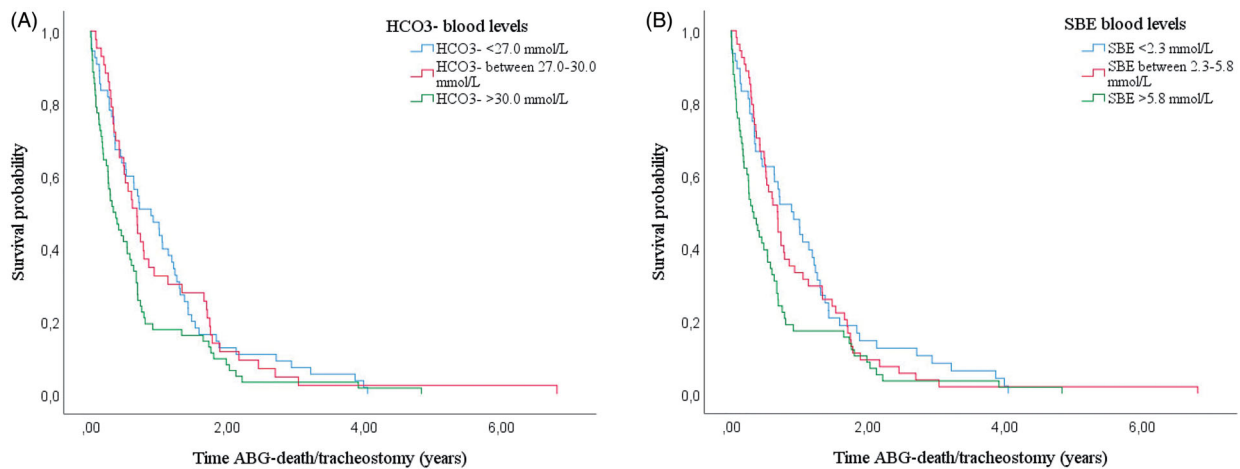


Figure 1. Kaplan–Meier curves: survival from time of post-NIVABG. Patients (*n* = 160) grouped according to HCO₃⁻ blood levels (a) and SBE blood levels (b). Both patients with HCO₃⁻ and SBE blood levels in the first and second tertile showed a longer survival than patients in the last tertile. In particular patients with HCO₃⁻ < 27.0 mmol/L and between 27.0 and 30.0 mmol/L showed a longer survival than patients with HCO₃⁻ > 30.0 mmol/L (respectively, 0.80 years, IQR 0.32–1.41 versus 0.32 years, IQR 0.10–0.72; *p* = 0.035 and 0.60 years, IQR 0.29–1.66 vs. 0.32 years, IQR 0.10–0.72; *p* = 0.041). Patients with SBE < 2.3 mmol/L and between 2.3 and 5.8 mmol/L showed a longer survival than patients with SBE > 5.8 mmol/L (respectively, 0.89 years, IQR 0.29–1.40 vs. 0.30 years, IQR 0.08–0.69; *p* = 0.028 and 0.61 years, IQR 0.30–1.37 vs. 0.30 years, IQR 0.08–0.69; *p* = 0.046).

When grouping patients in tertiles according to HCO₃⁻ and SBE levels, patients included in the first and in the second tertile showed a longer survival in NIV than patients in the last tertile (Figure 1(a,b)).

Survival in NIV was longer in patients with HCO₃⁻ blood levels <29.0 mmol/L and SBE <4.0 mmol/L (Figure 2).

Post-NIV ABG parameters did not show any significant difference between patients with bulbar

and spinal onset and between patients with and without bulbar involvement at time of NIV (Table 5). Bulbar onset did not influence survival in NIV (respectively for bulbar onset HR 1.145, 95% CI 0.812–1.614, $p=0.440$), while a severe bulbar involvement at time of NIV was associated with an increased risk for death/tracheostomy during ventilation (HR 1.949, 95% CI 1.109–3.425, $p=0.020$).

Although patients with bulbar onset showed a lower overall survival than patients with spinal onset (2.28 years, IQR 1.84–2.95 vs. 2.65 years, IQR 1.72–4.35, $p=0.041$, Figure 3(a)) their survival after the starting of NIV was not different (0.82 years, IQR 0.39–1.53 vs 0.67, IQR 0.32–1.47, $p=0.675$, Figure 3(b)).

Discussion

We investigated the role of ABG parameters after NIV start as predictor of both patients' adherence

to ventilatory therapy and survival. We found that after NIV start pCO₂ levels were not correlated to survival in ALS patients, and only HCO₃⁻ and SBE levels were predictive of death/tracheostomy. Specifically, when HCO₃⁻ blood levels were above 29 mmol/L and SBE above 4 mmol/L risk for death/tracheostomy was increased by more than 40% and survival significantly shortened.

The correlation between ABG parameters and survival was found to be stronger before NIV starting (8): this could be due to the real efficacy of ventilatory therapy, that can normalize pCO₂ and HCO₃⁻ blood levels if performed correctly, thus reducing the strength of correlation between ABG values and survival. The inverse correlation between pH and survival could be related to the chronic HCO₃⁻ increase in ALS patients with nocturnal hypoventilation (9); so a higher pH is a sign of chronic compensation during a respiratory failure of longer duration and thus a marker of worse prognosis in ALS. Indeed acidosis is not a

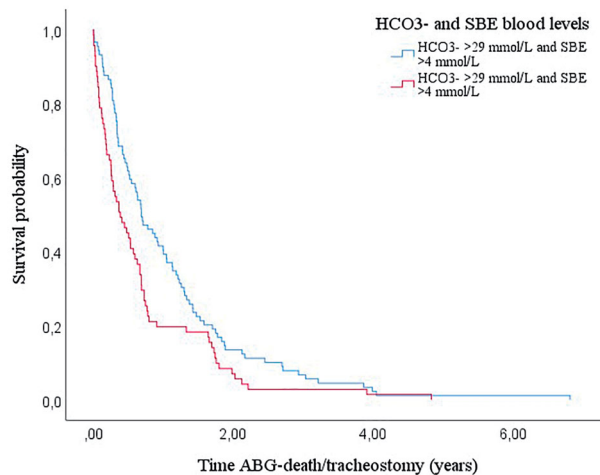


Figure 2. Kaplan–Meier curves: survival from time of post-NIVABG according to HCO₃⁻ and SBE cutoffs ($n=160$). Patients with HCO₃⁻ <29.0 mmol/L and SBE <4.0 mmol/L showed a longer survival than patients with both parameters increased (0.69 years, IQR 0.33–1.37 vs. 0.37 years, IQR 0.12–0.77; $p=0.013$).

Table 5. Comparison of post-NIV ABG parameters between patients with bulbar and spinal onset and between patients with and without bulbar involvement during ventilation.

	Bulbar onset ($n=54$) (median [IQR])	Spinal onset ($n=132$) (median [IQR])	* p Value
pCO ₂ (mmHg)	46.0 (42.1–51.0)	45.0 (40.0–49.2)	0.358
pO ₂ (mmHg)	75.5 (69.0–80.3)	75.8 (68.0–84.0)	0.471
HCO ₃ ⁻ (mmol/L)	28.4 (26.7–31.9)	28.1 (25.3–31.3)	0.325
SBE (mmol/L)	4.2 (2.3–7.2)	3.6 (1.0–7.1)	0.294
	Bulbar involvement ($n=131$) (median [IQR])	No bulbar involvement ($n=55$) (median [IQR])	p^*
pCO ₂ (mmHg)	45.0 (41.0–50.6)	45.0 (41.0–49.1)	0.900
pO ₂ (mmHg)	76.0 (69.0–83.0)	75.4 (68.0–83.0)	0.916
HCO ₃ ⁻ (mmol/L)	28.2 (25.7–31.7)	28.1 (25.2–31.0)	0.510
SBE (mmol/L)	6.3 (1.6–7.2)	3.6 (1.0–6.4)	0.395

No significant difference was found out between groups.

* p -value < 0.05 was considered significant.

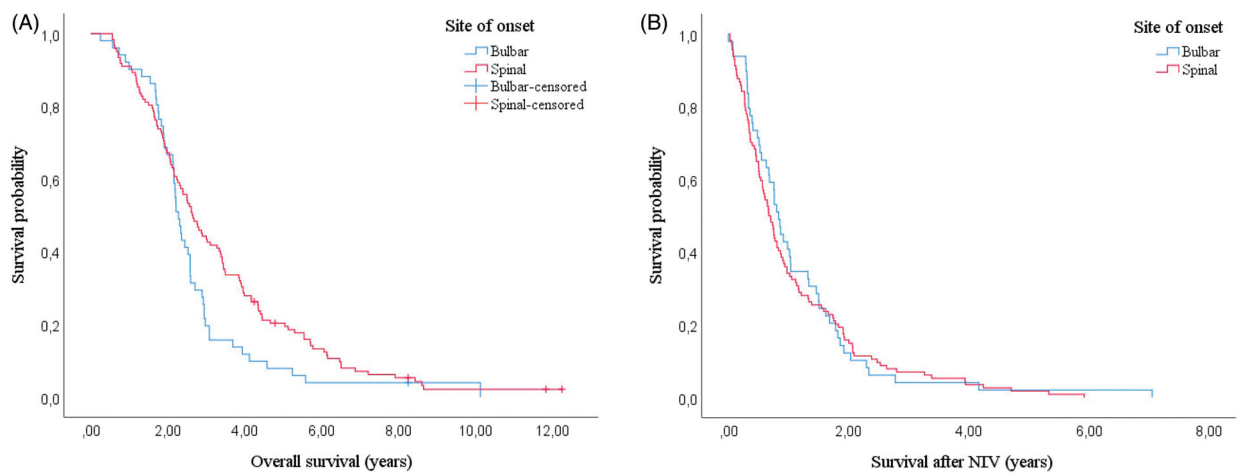


Figure 3. Kaplan–Meier curves: survival in bulbar onset and spinal onset patients ($n = 160$). Overall survival was lower for bulbar patients (2.28 years, IQR 1.84–2.95 vs. 2.65 years, IQR 1.72–4.35, $p = 0.041$, a) but survival in NIV was not statistically different (0.82 years, IQR 0.39–1.53 vs. 0.67, IQR 0.32–1.47, $p = 0.675$, b).

common event in our patients, being usually associated with an acute respiratory failure concomitant to pneumonia or other precipitant causes (10).

In a recent international survey about the monitoring of respiratory function among ALS tertiary centers, 37.8% (17/45) of European respondents reported that they always/nearly always use ABG, compared to only 1.4% (1/69) of US counterparts (11). In a study evaluating the role of ABG in predicting respiratory function and the necessity to start NIV, we found that when $p\text{CO}_2$ was >42 mmHg, $\text{HCO}_3^- >26$ mmol/L, or SBE >2 mmol/L there was a significant decline in FVC and an increase of risk for death/tracheostomy (8). In addition, an isolated increase of $\text{HCO}_3^-/\text{SBE}$ blood levels turned out to be a marker of nocturnal hypoventilation (NH), a frequently asymptomatic entity that prompts to start NIV.

The last European Federation of Neurological Societies (EFNS) guidelines recommend using FVC regularly for respiratory monitoring before and after NIV adaptation, while SNIP is recommended for bulbar patients (7). The National Institute for Care and Excellence (NICE) guidelines suggest performing respiratory function tests (oxygen saturation, FVC, SNIP/MIP) every 2–3 months and ABG analysis only in case of desaturation (12). About the role of ABG in post-NIV respiratory management, the American Academy of Neurology (AAN) guidelines mentioned only the importance of hypercapnia ($p\text{CO}_2 > 50$ mmHg) to indicate invasive ventilation starting (6). The German National Guideline for Treating Chronic Respiratory Failure guidelines for chronic respiratory failure indicate to monitor $p\text{CO}_2$ at least 1–2 times per year after NIV starting, as the gold standard to monitor ventilatory therapy adherence (13), even if values of daytime

$p\text{CO}_2$ cannot rule out NH, particularly in neuromuscular patients (14).

Based on our results, we showed that ABG is a useful tool to monitor mechanical ventilation compliance, and can predict patients' survival. $\text{HCO}_3^-/\text{SBE}$ levels are strictly related to patients' adherence and tolerance to ventilatory support; therefore, clinicians should pay attention when their blood levels are increased, even with $p\text{CO}_2$ normal values. Indeed, progressive respiratory decompensation in ALS patients leads to chronic respiratory acidosis that causes a compensatory increase in serum bicarbonate levels (15). A scarce adaptation/answer to NIV could lead to a nocturnal increase of $p\text{CO}_2$ and $\text{HCO}_3^-/\text{SBE}$ levels, but in the morning when ABG is usually performed, it is still possible to detect an increase in $\text{HCO}_3^-/\text{SBE}$ levels without a parallel increase of $p\text{CO}_2$, since $\text{HCO}_3^-/\text{SBE}$ levels do not decrease as fast as $p\text{CO}_2$ levels with daytime orthostatic breathing. Consequently, finding high $\text{HCO}_3^-/\text{SBE}$ levels even without hypercapnia should prompt the modification of ventilation settings, for example changing the type of mask or ventilation parameters, or increase in the duration of NIV usage. Adjusting NIV parameters may reduce nocturnal desaturations and improve prognosis (16,17).

Moreover, we found that, even if patients with bulbar onset show a lower overall survival than patients with spinal onset, their survival after the starting of NIV does not differ. Indeed, ABG parameters during ventilation did not differ between bulbar and spinal onset patients. Only the presence of a severe bulbar involvement at time of ventilation turned out to be a negative prognostic factor. This finding confirms that an intensive educational training and adaptation to NIV in a multidisciplinary setting increases compliance and tolerance also in patients with bulbar impairment (3). Therefore, even if bulbar impairment remains

a negative prognostic factor for ALS and a lower percentage of bulbar onset patients are able to adapt to ventilation, partly due to the higher prevalence of cognitive dysfunction in bulbar patients (18,19), NIV shows a similar benefit in all disease phenotypes.

Our study has some limitations. First, due to its retrospective nature, we could not compare ABG values to other pulmonary function tests, such as forced vital capacity (FVC), nocturnal oximetry or mechanical ventilator's recordings to confirm our data on NIV compliance. Second, due to the intrinsic difficulty to perform a complete neuropsychological evaluation in ALS patients with advanced disease, we could not include cognitive evaluation in our study.

Due to the importance of respiratory support, ventilation adherence is crucial in ALS patients: ABG evaluation, especially considering SBE and HCO₃⁻ blood levels, turned to be an inexpensive and informative tool to assess patients' compliance to NIV, to monitor pulmonary function, and to modify ventilator settings when necessary, in order to improve both quality of life and survival.

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Declaration of interest

Dr Manera, Dr Torrieri, Dr Moglia, Dr Canosa, Dr Vasta, Dr Palumbo, Dr Solero, Dr Ribolla, Dr Mattei and Dr Mora report no conflicts of interest. Prof Calvo has received research grant from Cytokinetics. Prof Chiò serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, and Cytokinetics.

The sponsor organizations had no role in data collections and analysis and did not participate to writing and approving the manuscript. The information reported in the manuscript has never been reported elsewhere.

Author contributions

Dr Manera has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Concept and design: Manera, Torrieri, Calvo, Chiò. *Acquisition, analysis, or interpretation of data:*

Manera, Torrieri, Moglia, Canosa, Vasta, Palumbo, Solero, Ribolla, Mattei, Mora, Calvo, Chiò. *Drafting of the manuscript:* Manera, Torrieri. *Critical revision of the manuscript for important intellectual content:* Manera, Torrieri, Moglia, Mattei, Mora, Calvo, Chiò. *Statistical analysis:* Manera, Torrieri. *Obtained funding:* Moglia, Mattei, Calvo, Chiò. *Administrative, technical, or material support:* Canosa, Vasta, Palumbo, Solero, Ribolla. *Supervision:* Mattei, Mora, Calvo, Chiò.

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Data availability statement

Data will be available upon request by interested researchers.

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