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The role of arterial blood gas analysis (ABG) in Amyotrophic Lateral Sclerosis respiratory monitoring

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There is still lack of consensus among different guidelines about the right timing for starting non-invasive mechanical ventilation (NIMV) in amyotrophic lateral sclerosis (ALS) [1-3]. The importance of spirometry as a reliable prognostic factor in ALS has been widely recognized; conversely, very few studies investigated the role of arterial blood gas analysis (ABG). Being respiratory failure the main cause of death in ALS, we aimed at investigating the role of ABG as proxy of Pulmonary Function Tests (PFTs) in a large cohort of ALS patients, identifying the best cut-off values for Forced Vital Capacity (FVC%), carbon dioxide (pCO₂), carbonate (HCO₃⁻) and standard base excess (SBE) to predict NIMV starting and survival.

We included 488 patients with concomitant ABGs, PFTs, and ALSFRS-r score, followed in the Turin ALS Center, resident in Piemonte and Valle d'Aosta, diagnosed between 2000 and 2015, excluding patients with severe pulmonary and kidney comorbidities. Descriptive statistic of the population is shown in Supplementary materials. Two-hundred and seventy-four patients (56.1%) underwent NIMV. Median time between ABG/PFT and NIMV initiation was 5.0 months (IQR 1.0-12.0). NIMV was started at a median FVC% value of 57.4% (IQR 44.2-73.6). Median overall survival after NIMV initiation was 225 days (IQR 104-491). Patients who did not undergo NIMV (N=214) were significantly older (68.6 years vs 64.9 years, p<0.001) and had a shorter overall median survival (2.3 years, IQR 1.5-3.5 vs 2.6 years, IQR 1.9-4.0, p=0.003).

ABG parameters showed a significant correlation with ALSFRS-r respiratory sub-score (for pCO₂ r= -0.301; for HCO₃⁻ r= -0.290; for SBE r= -0.291; p<0.001 for all parameters) and with FVC% values (for pCO₂ r= -0.350; for HCO₃⁻ r= -0.345; for SBE r= -0.325; p<0.001 for all parameters).

A significant decline in FVC% was recorded when pCO₂ exceeded 42 mmHg, or HCO₃⁻ exceeded 26 mmol/L, or SBE exceeded 2 mmol/L (Table 1). Moreover, patients who had a single HCO₃⁻ increase (>26 mmol/L) showed reduced FVC% values; a further significant decline in FVC% was observed when both pCO₂ and HCO₃⁻ were increased (Table 1). Therefore ABG parameters seem to predict pulmonary

function decline even when there is an isolated increase of HCO₃⁻ levels and also at pCO₂ levels lower than the values commonly used to prescribe NIMV.

ROC curves showed that the most sensitive and specific cut-offs for starting NIMV within 3 months were: 70% for FVC%, 42 mmHg for pCO₂, 26 mmol/L for HCO₃⁻, and 2 mmol/L for SBE (see Supplementary material). Interestingly, the sensitivity and specificity of ABG measures were not influenced by neither type of onset (bulbar/spinal) nor the presence of bulbar dysfunction at time of ABG.

ABG/PFT values were predictive of death/tracheostomy only in patients who did not undergo NIMV. Risk of death/tracheostomy increased significantly by 83.0% when pCO₂ reached 42 mmHg.

Taken together, our data indicate that the use of current guidelines for NIMV initiation could lead to a delayed treatment of respiratory failure in ALS patients, since we found a significant increase in death risk already when pCO₂ blood levels were above 42 mmHg and FVC values dropped below 80%.

Moreover, the current values of pCO₂ and FVC% used for NIMV indication have a reduced sensitivity for NIMV starting within 3 months in comparison with cut-offs of 42 mmHg for pCO₂ and of 80% for FVC%.

HCO₃⁻ elevation alone without significant pCO₂ elevation occurred in about 25% of our patients, being a day-time marker of nocturnal hypoventilation (NH). NH is the first sign of respiratory failure in neuromuscular disorders [4] and one of the most frequent sleep disturbances in ALS, which is sometimes underestimated [5]. The frequency of respiratory symptoms did not differ between patients with normal ABG and those who showed a single HCO₃⁻ increase. Respiratory symptoms became more common only when both pCO₂ and HCO₃⁻ increased (dyspnea in 53.1% and orthopnea in 42.0% of cases; p<0.001 for both). Based on these data, NH is a frequently asymptomatic entity, associated with a high risk for starting NIMV at 3 months (increase of HR by 54.7% and 45.9% when HCO₃⁻ and SBE were above 26.0 mmol/L and 2.0 mmol/L, respectively). As a compensatory mechanism, HCO₃⁻ elevation is related to a respiratory drive reduction with consequent worsening of hypercapnia. Current guidelines do not consider

blood HCO₃⁻ levels as a criterion to start ventilation [1,2,3]. According to our findings, after excluding any metabolic cause, we suggest that ALS patients could benefit from NIMV also in presence of an isolated increase of blood HCO₃⁻/SBE levels.

Survival analysis confirmed our data: patients with normal pCO₂ and HCO₃⁻ values at ABG survived longer than patients with normal pCO₂ and increased HCO₃⁻ (1.39 years, IQR 1.23-1.55 vs 0.87 years, IQR 0.73-1.02; p<0.001) and patients with increased pCO₂ and HCO₃⁻ levels (0.75 years, IQR 0.60-0.90; p<0.001, see Supplementary material).

The clinical-based retrospective nature of our study did not allow us to investigate other different PFTs, that have been proposed for respiratory function monitoring, such as maximal inspiratory/expiratory pressure (MIP/MEP) and/or sniff nasal inspiratory pressure (SNIP). However, their use is less considered than FVC/SVC in respiratory assessment and particularly in clinical trials.

ABG, though being minimally invasive, is a sensitive, easy to perform, and inexpensive tool for monitoring respiratory function in ALS patients, and turned out to correlate with FVC. Unlike other PFTs, ABG does not require patient collaboration and is not influenced by bulbar involvement. Moreover, it can detect NH, a clinical condition which is frequently underestimated in patients with neuromuscular disorders.

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Author Contributions

Dr Manera had 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, Viglione, Daviddi, Matteoni,

Solero, Palumbo, Vasta, Canosa, D'Ovidio, Focaraccio, 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, D'Ovidio.

Obtained funding: Moglia, Mattei, Calvo, Chiò. *Administrative, technical, or material support:* Viglione,

Daviddi, Matteoni, Solero, Palumbo, Vasta, Canosa, Focaraccio. *Supervision:* Mora, Calvo, Chiò.

Conflict of Interest/Disclosures

Conflict of interest: Dr Manera, Dr Torrieri, Dr Moglia, Dr Viglione, Dr Daviddi, Dr Matteoni, Dr Solero, Dr Palumbo, Dr Vasta, Dr Canosa, Dr D'Ovidio, Dr Focaraccio, 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, and Cytokinetics.

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Table 1. Median FVC% values for different values of pCO₂, HCO₃⁻ and SBE and for combined pCO₂/HCO₃⁻ cut-offs. Comparison of FVC% values at modifying of each ABG parameter. Mann-Whitney U test comparing each ABG parameter range to the previous one (p value < 0.05 was considered significant and significant values are written in bold).

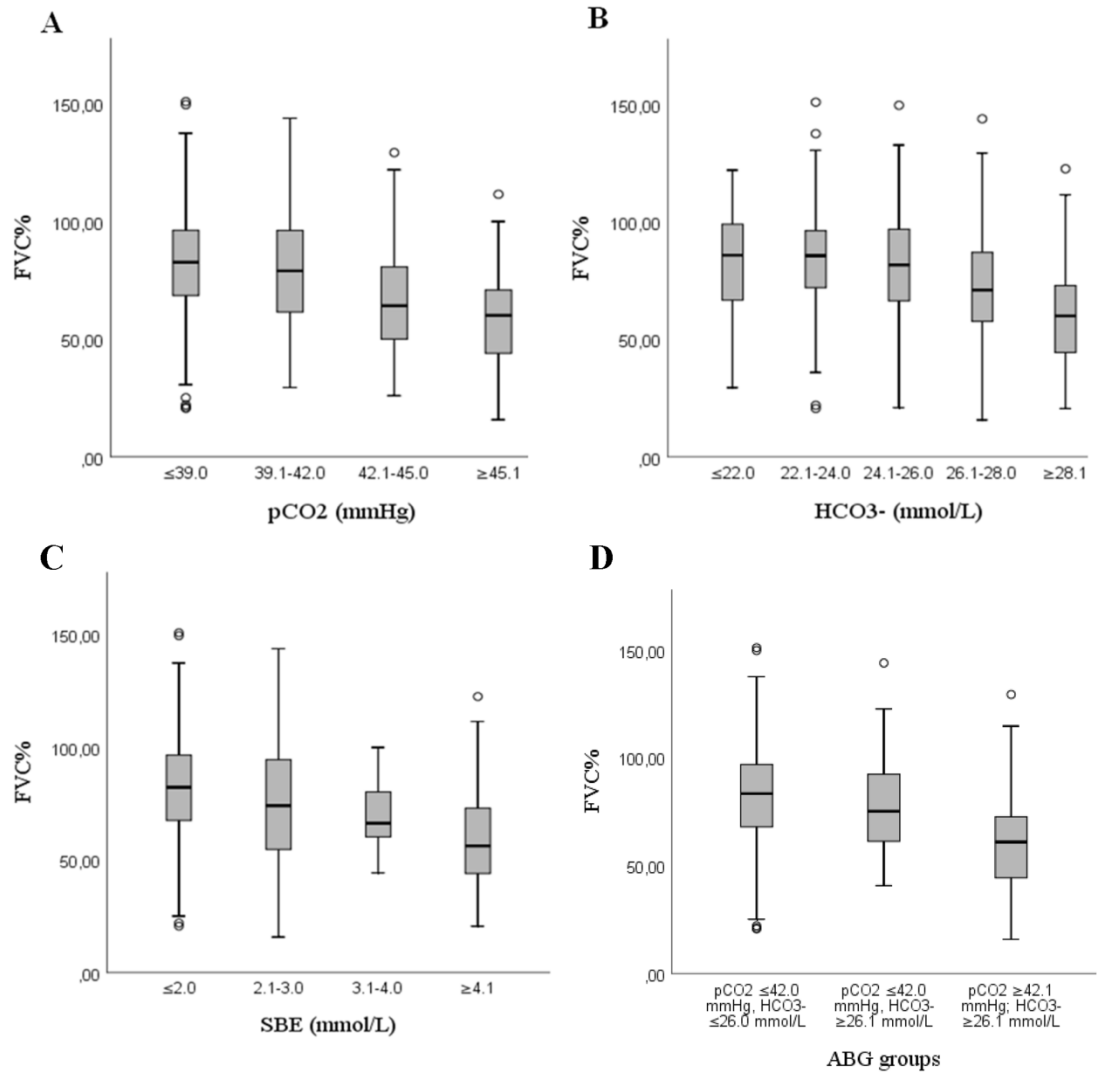
ABG parameter	FVC% (Median value, IQR)	p*
pCO₂		
≤39.0 mmHg	82.7 (68.5-96.4)	
39.1-42.0 mmHg	79.0 (60.7-96.3)	0.205
42.1-45.0 mmHg	64.2 (49.6-81.3)	0.007
>45.0 mmHg	60.1 (43.2-71.0)	0.386
HCO₃⁻		
≤22.0 mmol/L	85.7 (65.4-99.2)	
22.1-24.0 mmol/L	85.6 (71.8-96.4)	0.899
24.1-26.0 mmol/L	81.7 (66.2-97.3)	0.256
26.1-28.0 mmol/L	71.0 (57.6-87.2)	<0.001
>28.0 mmol/L	60.0 (44.4-73.2)	<0.001
SBE		
≤2.0 mmol/L	82.3 (67.4-96.7)	
2.1-3.0 mmol/L	74.1 (54.5-95.0)	0.028
3.1-4.0 mmol/L	66.3 (60.3-81.0)	0.042
>4.0 mmol/L	56.2 (43.7-73.5)	0.014
Combined pCO₂/HCO₃⁻ (pCO₂ cut-off = 45 mmHg)		
pCO ₂ ≤45.0 mmHg & HCO ₃ ⁻ ≤ 26.0 mmHg	83.4 (67.9-97.0)	
pCO ₂ ≤ 45.0 mmHg & HCO ₃ ⁻ > 26.0 mmHg	70.5 (56.0-88.0)	<0.001
pCO ₂ >45.0 mmHg & HCO ₃ ⁻ > 26.0 mmHg	60.0 (42.8-71.0)	<0.001
Combined pCO₂/HCO₃⁻ (pCO₂ cut-off = 42 mmHg)		
pCO ₂ ≤ 42.0 mmHg & HCO ₃ ⁻ ≤ 26.0 mmHg	83.4 (67.9-97.9)	
pCO ₂ ≤ 42.0 mmHg & HCO ₃ ⁻ > 26.0 mmHg	75.2 (61.0-92.4)	0.008
pCO ₂ > 42.0 mmHg & HCO ₃ ⁻ > 26.0 mmHg	60.9 (44.3-72.8)	<0.001

eTable 1. Demographic characteristics and ABGs/PFTs values. Patients who underwent NIMV vs patients who did not undergo NIMV. Differences of discrete and continuous variables were analyzed using the χ^2 test and Mann-Whitney U test respectively. Δ ALSFRS-R = (48- ALSFRS-R score at ABG)/disease duration.

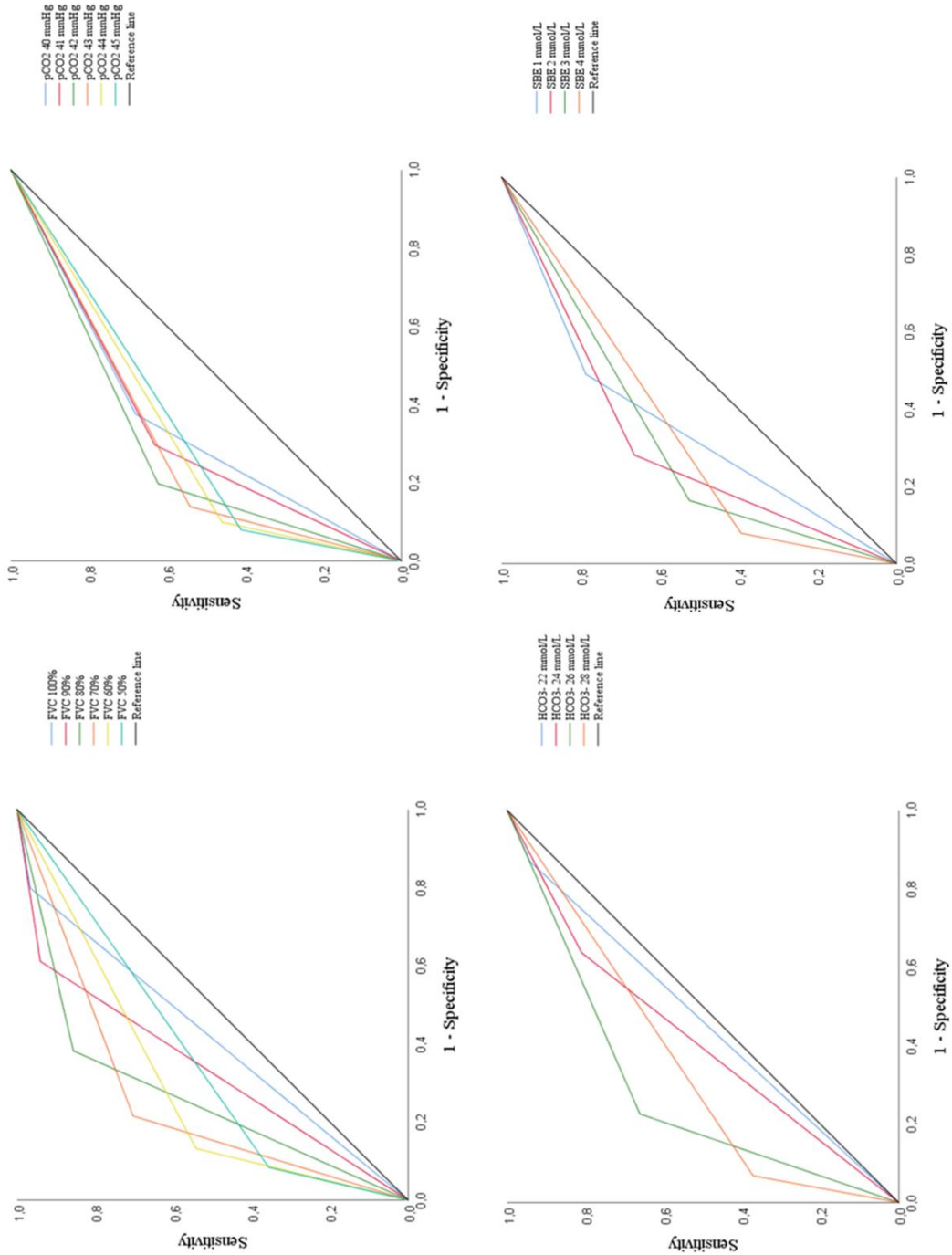
	All patients	NIMV	No NIMV	
	<i>Median (IQR)</i>	<i>Median (IQR)</i>	<i>Median (IQR)</i>	<i>p*</i>
Age at onset (years)	66.3 (59.0-72.1)	64.9 (57.4-70.2)	68.6 (61.1-73.0)	<0.001
FVC (%)	75.8 (57.9-92.3)	74.6 (54.8-89.6)	79.2 (61.7-92.3)	0.009
FEV1 (%)	77.8 (58.5-95.6)	75.9 (56.4-93.8)	81.4 (61.3-97.1)	0.051
pH	7.43 (7.41-7.44)	7.42 (7.40-7.44)	7.43 (7.41-7.45)	0.005
pCO2 (mmHg)	40.0 (37.0-43.0)	40.8 (38.0-44.7)	39.0 (36.2-41.5)	<0.001
pO2 (mmHg)	81.0 (73.8-87.0)	80.0 (72.6-85.7)	82.1 (76.0-87.5)	0.020
HCO3- (mmol/l)	25.5 (23.7-27.3)	25.7 (24.0-28.0)	25.0 (23.5-26.6)	<0.001
SBE (mmol/l)	1.37 (-0.20-3.12)	1.66 (0.03-3.66)	0.85 (-0.54-2.65)	0.001
Δ ALSFRS-R (points/month)	0.55 (0.33-1.00)	0.52 (0.31-0.92)	0.62 (0.33-1.07)	0.095
Overall survival (years)	2.5 (1.7-3.8)	2.6 (1.9-4.0)	2.3 (1.5-3.5)	0.003
Onset-ABG/PFT interval (years)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	1.1 (0.7-1.8)	0.814
ABG/PFT-death/tracheostomy interval (years)	1.2 (0.6-2.0)	1.4 (0.7-2.0)	0.9 (0.5-1.8)	<0.001
	<i>n (%)</i>	<i>n (%)</i>	<i>n (%)</i>	<i>p[#]</i>
Sex				
Male	273 (55.9%)	166 (60.6%)	107 (50.0%)	0.019
Female	215 (44.1%)	108 (39.4%)	107 (50.0%)	
Type of onset				
Bulbar onset	170 (34.8%)	90 (32.8%)	80 (37.4%)	0.064
Spinal onset	318 (65.2%)	184 (67.2%)	134 (62.6%)	
Respiratory symptoms at ABG/PFT				
Dyspnea (ALSFRS-R 10 < 4)	131 (26.8%)	84 (30.7%)	47 (22.0%)	0.032
Orthopnea (ALSFRS-R 11 < 4)	103 (21.1%)	66 (24.1%)	37 (17.3%)	0.068
Both (ALSFRS-R 10 & 11 < 4)	92 (18.9%)	61 (22.3%)	31 (14.5%)	0.029
No symptoms	346 (70.9%)	185 (67.5%)	161 (75.2%)	0.063
Total	488 (100%)	274 (56.1%)	214 (43.9%)	

* Significant p values (<0.05) are written in bold

eFigure1. Box-plot for median value of FVC% for different ABG parameters (pCO₂, HCO₃⁻, SBE; figures A, B, C) and for different ABG groups (figure D).



eFigure2. ROC curves for different cut-off values of FVC%, pCO₂, HCO₃⁻ and SBE. Sensitivity and specificity for starting NIMV at 3 months from ABG/PFT.



eTable2. Sensitivity and specificity for NIMV starting in 3 months. Best cut-off values for FVC%, pCO₂, HCO₃⁻ and SBE based on Youden Index and area under the curve (AUC). Youden Index was calculated using Youden J statistic formula (J = sensitivity + specificity – 1). The best value for each parameter are written in bold. * p-values <0.05 was considered as significant.

Parameter	Cuts-off	Sensitivity	Specificity	Youden Index	AUC	p*
<i>FVC (%)</i>	100	96.6%	20.0%	0.166	0.583	0.021
	90	94.1%	38.6%	0.327	0.663	<0.001
	80	85.6%	61.4%	0.470	0.735	<0.001
	70	70.3%	77.9%	0.482	0.741	<0.001
	60	54.2%	86.2%	0.404	0.702	<0.001
	50	35.6%	91.7%	0.273	0.637	<0.001
<i>pCO₂ (mmHg)</i>	40.0	68.0%	62.7%	0.307	0.654	<0.001
	41.0	63.1%	70.6%	0.337	0.669	<0.001
	42.0	62.3%	80.4%	0.427	0.713	<0.001
	43.0	54.1%	86.3%	0.404	0.702	<0.001
	44.0	45.9%	90.2%	0.361	0.680	<0.001
	45.0	41.0%	92.2%	0.332	0.666	<0.001
<i>HCO₃⁻ (mmol/L)</i>	22.0	94.2%	13.0%	0.007	0.536	0.309
	24.0	81.0%	36.3%	0.173	0.586	0.015
	26.0	66.1%	77.4%	0.435	0.718	<0.001
	28.0	37.2%	93.2%	0.304	0.652	<0.001
<i>SBE (mmol/L)</i>	1.0	78.7%	51.0%	0.297	0.648	<0.001
	2.0	66.4%	71.9%	0.383	0.691	<0.001
	3.0	52.5%	83.7%	0.362	0.681	<0.001
	4.0	39.3%	92.2%	0.315	0.658	<0.001

eTable3. Comparison of AUC values in ROC curves (diagnostic ability of discrimination for starting NIMV at 3 months) between patients with bulbar/spinal onset and between bulbar/no bulbar dysfunction at time of ABG/PFT. No significant differences were found in AUC subdividing patients by site of onset and by bulbar involvement at time of ABG/PFT performance.

Parameter	AUC		p*
	Bulbar onset	Spinal onset	
<i>pCO2</i>	0.752	0.702	0.420
<i>HCO3-</i>	0.761	0.716	0.466
<i>SBE</i>	0.755	0.709	0.458
<i>FVC%</i>	0.772	0.768	0.936
	Bulbar dysfunction	No bulbar dysfunction	
<i>pCO2</i>	0.691	0.770	0.180
<i>HCO3-</i>	0.708	0.773	0.255
<i>SBE</i>	0.703	0.758	0.355
<i>FVC%</i>	0.746	0.813	0.164

AUC: Area under the curve

* p values was considered significant when <0.05.

eTable4. Hazard ratios (HR) for death/tracheostomy and NIMV starting, divided by each cut-off value for CO₂, HCO₃⁻, SBE blood levels and FVC% in patients who underwent and did not undergo NIMV. Cox proportional hazard models adjusted for sex, age at onset, site of onset (bulbar/spinal), time between onset and ABG/PFT, ALSFRS-r items 10 and 11. * p-values <0.05 was considered as significant and written in bold

	NO NIMV (n=214)		NIMV (n=274)			
	Risk for death/tracheostomy		Risk for death/tracheostomy		Risk for NIMV	
	HR (95% CI)	p*	HR (95% CI)	p*	HR (95% CI)	p*
<i>pCO₂ cut-off</i>						
40 mmHg	1.362 (1.007-1.842)	0.045	1.058 (0.815-1.373)	0.674	1.428 (1.100-1.854)	0.007
41 mmHg	1.397 (1.009-1.935)	0.044	1.017 (0.779-1.328)	0.901	1.352 (1.034-1.768)	0.027
42 mmHg	2.227 (1.525-3.254)	< 0.001	1.110 (0.841-1.465)	0.460	1.638 (1.233-2.176)	0.001
43 mmHg	3.501 (2.266-5.410)	< 0.001	1.170 (0.876-1.563)	0.288	1.815 (1.343-2.453)	< 0.001
44 mmHg	3.716 (2.253-6.128)	< 0.001	1.026 (0.748-1.408)	0.872	1.638 (1.184-2.267)	0.003
45 mmHg	4.558 (2.586-8.035)	< 0.001	1.135 (0.819-1.573)	0.448	1.704 (1.219-2.381)	0.002
<i>HCO₃⁻ cut-off</i>						
22 mmol/L	1.471 (0.959-2.256)	0.077	0.859 (0.555-1.328)	0.494	1.065 (0.680-1.668)	0.783
24 mmol/L	1.315 (0.984-1.757)	0.064	1.052 (0.788-1.403)	0.732	1.006 (0.726-1.394)	0.970
26 mmol/L	1.509 (1.077-2.114)	0.017	1.123 (0.860-1.467)	0.395	1.553 (1.181-2.040)	0.002
28 mmol/L	2.562 (1.318-4.981)	0.006	1.027 (0.726-1.454)	0.880	1.611 (1.124-2.309)	0.009
<i>SBE cut-off</i>						
1.0 mmol/L	1.362 (1.017-1.825)	0.038	1.039 (0.790-1.366)	0.784	1.076 (0.797-1.452)	0.632
2.0 mmol/L	1.555 (1.149-2.106)	0.004	1.071 (0.820-1.397)	0.616	1.535 (1.177-2.000)	0.002
3.0 mmol/L	1.624 (1.132-2.330)	0.008	1.169 (0.882-1.549)	0.277	1.328 (1.002-1.760)	0.048
4.0 mmol/L	2.665 (1.660-4.278)	< 0.001	1.034 (0.745-1.435)	0.841	1.476 (1.054-2.069)	0.024
<i>FVC% cut-off</i>						
100%	1.556 (1.106-2.189)	0.011	0.796 (0.533-1.188)	0.264	1.799 (1.223-2.648)	0.003
90%	1.728 (1.286-2.321)	< 0.001	0.882 (0.627-1.241)	0.472	2.189 (1.605-2.985)	< 0.001
80%	2.147 (1.595-2.890)	< 0.001	1.228 (0.919-1.640)	0.165	2.611 (1.960-3.477)	< 0.001
70%	2.048 (1.505-2.789)	< 0.001	1.134 (0.851-1.512)	0.390	2.920 (2.208-3.862)	< 0.001
60%	1.927 (1.333-2.784)	< 0.001	1.146 (0.852-1.542)	0.367	2.296 (1.666-3.164)	< 0.001
50%	2.665 (1.704-4.166)	< 0.001	1.113 (0.799-1.550)	0.526	1.872 (1.288-2.722)	< 0.001

eFigure3. Kaplan-Meier curves for median survival from time of ABG. Patients were grouped according to ABG values of pCO₂ and HCO₃⁻ (pCO₂ and HCO₃⁻ were considered increased if > 45 mmHg and >26 mmol/L, respectively). Patients who showed normal pCO₂ and HCO₃⁻ levels showed a longer survival than patients with a single HCO₃⁻ increase (1.39 years vs 0.87 years, log-rank test p <0.001) and those with both pCO₂ and HCO₃⁻ increased (0.75 years, log rank test p <0.001).

