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ORIGINAL ARTICLE

Use of the combination of spirometry, arterial blood gas analysis and overnight oximetry to predict the outcomes of patients affected by motor neuron disease: The Milan-Torin respiratory score (Mi-To-RS)

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Abstract

Background and purpose: The use of multiple tests, including spirometry, arterial blood gas (ABG) analysis and overnight oximetry (OvOx), is highly recommended to monitor the respiratory function of patients with motor neuron disease (MND). In this study, we propose a composite score to simplify the respiratory management of MND patients and better stratify their prognosis.

Materials and Methods: We screened the clinical charts of 471 non-ventilated MND patients referred to the Neuro-rehabilitation Unit of the San Raffaele Scientific Institute of Milan (January 2001–December 2019), collecting spirometric, ABG and OvOx parameters. To evaluate the prognostic role of each measurement, univariate Cox regression for death/tracheostomy was performed, and the variables associated with survival were selected to design a scoring system. Univariate and multivariate Cox regression analyses were then carried out to evaluate the prognostic role of the score. Finally, results were replicated in an independent cohort from the Turin ALS Center.

Results: The study population included 450 patients. Six measurements were found to be significantly associated with survival and were selected to design a scoring system (maximum score = 8 points). Kaplan–Meier analysis showed significant stratification of survival and time to non-invasive mechanical ventilation adaptation according to score values, and multivariate analysis confirmed the independent effect of the respiratory score on survival of each cohort.

Conclusion: Forced vital capacity, ABG and OvOx parameters provide complementary information for the respiratory management and prognosis of MND patients and the combination of these parameters into a single score might help neurologists predict prognosis and guide decisions on the timing of the implementation of different diagnostic or therapeutic approaches.

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ALS, amyotrophic lateral sclerosis, blood gas analysis, neuromuscular diseases, NIMV, non-invasive ventilation, prognosis, respiratory failure, spirometry

INTRODUCTION

Motor neuron disease (MND) encompasses a heterogeneous group of neurological disorders affecting the upper and lower motor neurons, causing relentless progressive spasticity and muscle weakness [1, 2]. When the disease involves the respiratory muscles, progressive respiratory failure occurs, which represents the main cause of death for MND patients, occurring 3–5 years after symptom onset. Available respiratory support includes non-invasive mechanical ventilation (NIMV) and, eventually, a tracheostomy placement, followed by invasive mechanical ventilation, which can extend survival, on average, by 2 years [3]. Careful monitoring of respiratory function with regular respiratory tests (RTs) is highly recommended for the appropriate management of MND patients in order to assess the need for NIMV adaptation, which has been shown to improve patients' quality of life and median survival, and in order to predict prognosis [4, 5]. Among RTs, there is no single test or measurement which can unequivocally determine the respiratory function of a patient, and usually multiple tests are suggested [3, 6–9]. Forced vital capacity (FVC%) is the most commonly used measure of respiratory function in MND and is considered a strong predictor of survival and a criterion for initiation of NIMV, even though there is no definite agreement on the specific individual threshold for NIMV indication [3, 4, 10, 11]. Additionally, FVC and slow vital capacity (SVC) are consistently recognized as a meaningful secondary outcome measure in amyotrophic lateral sclerosis (ALS) clinical trials [12].

Arterial blood gas (ABG) analysis reflects the efficacy of gas interchange and is useful for detecting hypoventilation through the indicators of chronic respiratory acidosis (low pH and high carbon dioxide, pCO_2, in association with high carbonate, HCO_3^-, and standard base excess [SBE]) [13]. Although ABG abnormalities are generally a late finding [11], it has recently been suggested that isolated HCO_3^- elevation, in the absence of pCO_2 elevation, could be a red flag for nocturnal hypoventilation (NH), which may precede symptoms of diurnal hypercapnia, and may be considered an additional marker in patients who could benefit from NIMV adaptation [13]. Overnight oximetry (OvOx) is a simple and non-invasive test that can be used to evaluate the presence of nocturnal desaturations and sleep apneas, which are commonly associated with MND, and, is therefore frequently performed in clinical practice [14, 15].

Although a combination of FVC, ABG and OvOx parameters seem to increase sensitivity to detect NH [14], no previous study has evaluated the combined role of these tests in respiratory management and survival. The aim of the present study, therefore, was to evaluate the prognostic role of the combined evaluation of OvOx and ABG measurements in addition to FVC in a large cohort of MND patients. Additionally, we propose a composite score with the potential to simplify the assessment of patient prognosis based on their respiratory function.

METHODS

Patient data collection

In this retrospective study, approved by our local ethics committee, we screened the clinical charts of 471 MND patients recruited in the Neuro-rehabilitation Unit of the San Raffaele Scientific Institute of Milan from January 2001 to December 2019 (Figure S1), for each of whom an FVC value was available.

Diagnosis of MND was established according to the revised El Escorial criteria (r-EEC) [16]; additionally, a subgroup of patients with flail arm, flail leg and pure lower motor neuron phenotypes who did not fulfil the r-EEC were grouped into an additional category called "unclassified", an approach adopted in previous reports [17]. For each patient the following data were collected: sex, age at symptom onset, diagnostic delay, site of onset (bulbar or spinal), clinical phenotype [18], revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALS-FRS-R) score at evaluation [19], and presence of dementia [20]. Disease progression rate (ΔALS-FRS), was calculated using the following formula (48 − ALS-FRS)/time from onset to evaluation (months) [21].

Patients were followed up with regular neurological observation and periodic telephone calls in order to collect information on NIMV, tracheostomy and date of death. Survival was defined as time from symptom onset to death/tracheostomy or censoring day (last day of follow-up was 31 December 2019).

Respiratory tests

The FVC data were collected from spirometry performed during hospitalization by an expert pneumologist and including only tests with at least three maneuvers; the highest value was retained. FVC was expressed as an absolute value, in liters, and as a percentage (FVC%), calculated in accordance with the formulas of Goldman and Becklake. Monthly decline in FVC%, termed ΔFVC%, was calculated as follows: (100 − FVC%)/time from onset to evaluation (months).

Arterial blood samples were drawn from the radial artery, with the patient in the seated or supine position breathing room air, usually in the early morning. For the ABG analysis, we collected the following measurements: arterial pH, partial arterial pressure of oxygen (pO_2), pCO_2, HCO_3^- and SBE.

The OvOx was performed in the patient's room, on room air, for a duration of at least 8 h. The following data were obtained: mean

percentage saturation (MPS), average minimum saturations (AMS), percentage of recording time spent with oxygen saturation at <90% (T90) and oxygen desaturation index (ODI), that is, the number of times that oxygen saturation decreases per hour.

Statistical analysis

Normality data distribution was explored with the Shapiro–Wilk test. Baseline characteristics were summarized using standard descriptive statistics and presented as median and interquartile range (IQR) for quantitative measures, and number (*N*) and percentage (%) for categorical variables. Relationships between FVC%, ABG and OvOx parameters were analyzed using the Pearson test. We applied two-tailed unpaired Mann–Whitney *U* tests and Kruskal–Wallis tests with Bonferroni post hoc comparison to verify differences between two or more groups, respectively. Survival curves were estimated using Kaplan–Meier analysis and compared using the log rank test, while univariate Cox regression was carried out to derive unadjusted hazard ratios (HRs) for death/tracheostomy of each respiratory measurement. Statistical uncertainty was expressed as 95% confidence interval (CI). Cox multivariate analysis, corrected for well-known prognostic variables (age at onset, site of onset, diagnostic certainty according to r-EEC, ΔALS-FRS, dementia and diagnostic delay) [4], was subsequently carried out in order to evaluate the role of respiratoy variables as independent factors affecting survival and to estimate their proportional HRs. To avoid collinearity bias between measurements showing a high correlation coefficient and to develop a simple prognostic score easily applicable in clinical practice, the respiratory variables found to be associated with survival were finally aggregated into a scoring system for the assessment of patient prognosis accordingly to respiratory function. To confirm the prognostic role of the respiratory variables, we next replicated our findings in an independent control cohort which included 180 MND patients from the Piemonte and Valle d'Aosta Register for ALS (Table S1). All statistical analyses were performed using IBM SPSS 21.0. All tests were two-tailed and statistical significance was set at $p < 0.05$.

RESULTS

The overall study population included 471 MND patients. Patients ($n = 21$) with previous indication for NIMV or affected by significant kidney or lung comorbidities, or whose RTs were not available, were excluded from the study. In this study, we therefore included 450 patients, for each of whom an FVC% value was available. ABG data for 188 and OvOx data for 265 of these 450 patients, performed during the same hospitalization, were available. The demographic, clinical characteristics and median respiratory measurements of our sample are summarized in Table 1. RTs were performed at a median (IQR) of 15.5 (9.0–28.0) months from symptoms onset.

TABLE 1 Descriptive statistics of the Milan motor neuron disease cohort.

Sex, *n* (%)	
Man	245 (54.4)
Woman	205 (45.6)
Age at onset, median (IQR) years	62.0 (55.0–68.0)
Diagnostic delay, median (IQR) months	10.0 (6.0–19.0)
Disease duration, median (IQR) months	15.5 (9.0–28.0)
Site of onset, *n* (%)	
Bulbar	100 (22.2)
Spinal	350 (78.8)
Phenotype, *n* (%)	
Classic ALS	210 (46.7)
Bulbar	70 (15.6)
Flail arm	11 (2.4)
Flail leg	28 (6.2)
PLMN	34 (7.6)
Pyramidal	53 (11.8)
PUMN	36 (8.0)
Respiratory	2 (0.4)
Dementia, *n* (%)	
Yes	36 (8.0)
El Escorial criteria, *n* (%)	
Definite ALS	119 (26.4)
Probable ALS	146 (32.4)
Possible ALS	70 (15.6)
Probable laboratory-supported ALS	78 (17.3)
Unclassified	37 (8.2)
FVC%, median (IQR)	77.0 (59.0–95.0)
Δ FVC%, median (IQR)	1.1 (0.2–3.1)
ABG measurement, median (IQR)	
pCO_2	40.9 (38.4–44.7)
HCO_3^-	26.1 (24.9–28.2)
SBE	1.7 (0.5–3.4)
OvOx, median (IQR)	
MPS	93.2 (92.0–94.8)
T90	1.0 (0.0–7.0)
ODI	8.1 (5.1–12.2)
AMS	90.9 (89.0–92.2)
NIMV, *n* (%)	206 (45.8)
Death or tracheostomy, *n* (%)	362 (80.4)

Abbreviations: ABG, arterial blood gas; ALS, amyotrophic lateral sclerosis; AMS, average minimum saturations; FVC, forced vital capacity; HCO_3^-, carbonate; IQR, interquartile range; MPS, mean oxygen percentage saturation; *n*, number; NIMV, non-invasive mechanical ventilation; ODI, oxygen desaturation index; OvOx, overnight oximetry; pCO_2, carbon dioxide; PLMN, pure lower motor neuron; PUMN, pure upper motor neuron; SBE, standard base excess; T90, percentage of recording time spent with oxygen saturation at <90%.

We first explored correlations among RT variables: FVC% showed a moderate correlation with ABG parameters (pCO_2: $r=-0.322$, HCO_3^-: $r=-0.348$, SBE: $r=-0.319$; $p<0.05$ for all parameters) and a weak correlation with OvOx measurements (T90: $r=-0.143$, AMS: $r=0.165$; $p<0.05$ for all parameters) except for MPS and ODI ($p>0.05$). No significant correlation between ABG and OvOx parameters was observed, apart from a weak correlation between AMS and pCO_2 ($r=-0.165$, $p<0.05$). ALS-FRS-R respiratory subscore showed a moderate correlation with both FVC% ($r=0.374$; $p<0.05$) and ABG parameters (pCO_2: $r=-0.374$, HCO_3^-: $r=-0.410$, SBE: $r=-0.342$; $p<0.05$ for all parameters), as well as a weak correlation with OvOx measurements (T90: $r=-0.139$, AMS: $r=0.161$; $p<0.05$ for all parameters). FVC%, SBE and ODI were the only respiratory measurements that were significantly correlated with ΔALS-FRS-R (FVC%: $r=-0.607$, SBE: $r=0.208$, ODI: $r=0.198$; $p<0.05$ for all parameters [Table 2]).

The Mann–Whitney *U* test disclosed a significant decline in FVC% when pCO_2 was >45 mmHg, HCO_3^- was >28 mmol/L, SBE was >2 mmol/L, T90 was >5%, MPS was <91% or AMS was <88% ($p<0.05$). Moreover, comparison between ABG and OvOx parameters showed that pCO_2, HCO_3^- and SBE were significantly higher when T90 was >5%, MPS was <91% and AMS was <88% ($p<0.05$ for all parameters [Tables 3 and 4]).

Kaplan–Meier survival analysis, together with Cox univariate analysis, are summarized in Table 5. Survival analysis revealed a significant risk stratification for patients showing a reduction of FVC%, with a shorter survival in lower FVC% interquartile groups (Mantel–Cox; $\chi^2=93.5$, $p<0.05$; FVC% 95%–76%: HR 1.9, 95% CI 1.4–2.6; FVC% 75%–58%: HR 2.5, 95% CI 1.9–3.4; FVC% <58%: HR 4.2, 95% CI 3.1–5.8). A significant stratification in survival curves was also observed for patients showing ΔFVC% >2 (Mantel–Cox; $\chi^2=73.6$, $p<0.05$; HR 2.5, 95% CI 2.0–3.1); $pCO_2>45$ mmHg (Mantel–Cox; $\chi^2=7.0$, $p<0.05$; HR 1.6, 95% CI 1.1–2.3), $HCO_3^->24$ mmol/L (Mantel–Cox; $\chi^2=11.1$, $p<0.05$; HR 2.1, 95% CI 1.3–3.7), SBE >2 mmol/L (Mantel–Cox; $\chi^2=6.3$, $p<0.05$; HR 1.5, 95% CI 1.1–2.1) and MPS <91% (Mantel–Cox; $\chi^2=4.1$, $p<0.05$; HR 1.5, 95% CI 1.0–2.1). No significant effect on survival was observed for ABG pO_2 levels and for T90, AMS and ODI OvOx measurements, therefore, these factors were not considered in subsequent analyses.

Prognostic score

The following respiratory variables were associated with survival and consequently selected to design a scoring system: FVC%, ΔFVC%, HCO_3^-, pCO_2, SBE and MPS; 0–4 points were assigned for spirometric values, 0–3 points were assigned for ABG values and 0–1 point for OvOx values. For ABG parameters, we decided to select the cut-off of 26 mmol/L for HCO_3^- since this value is widely considered a threshold between physiological and pathological conditions [13]. In the final model, we assigned 0–3 points for each FVC% interquartile group, an additional point for ΔFVC% >2 points/month and 1 point whenever the following cut-offs were exceeded: $HCO_3^->26$ mmol/L,

TABLE 2 Pearson correlation among different respiratory measurements and ALS-FRS-R scale of the Milan motor neuron disease cohort.

		FVC%	pCO_2	HCO_3^-	SBE	MPS	AMS	$T<90\%$	ODI	ALS-FRS-R respiratory subscore	ΔALS-FRS-R
FVC%	*r*	1	−0.322*	−0.348*	−0.319*	0.141	0.165*	−0.143*	0.018	0.374*	−0.607*
pCO_2	*r*	−0.322*	1	0.894*	0.752*	0.003	−0.165*	0.087	0.001	−0.374*	0.113
HCO_3^-	*r*	−0.348*	0.894*	1	0.933*	−0.035	−0.152	0.107	0.067	−0.410*	0.177
SBE	*r*	−0.319*	0.752*	0.933*	1	−0.051	−0.094	0.069	0.072	−0.342*	0.208*
MPS	*r*	0.141	0.003	−0.035	−0.051	1	0.081	−0.062	0.003	0.052	−0.089
AMS	*r*	0.165*	−0.165*	−0.152	−0.094	0.081	1	−0.529*	−0.293*	0.161*	−0.135
T90	*r*	−0.143*	0.087	0.107	0.069	−0.062	−0.529*	1	0.198*	−0.139*	0.018
ODI	*r*	0.018	0.001	0.067	0.072	0.003	−0.293*	0.198*	1	−0.123	0.198*
ALS-FRS-R resp- subscore	*r*	0.374*	−0.374*	−0.410*	−0.342*	0.052	0.161*	−0.139*	−0.123	1	−0.583*
Δ ALS-FRS-R	*r*	−0.607*	0.113	0.177	0.208*	−0.089	−0.135	0.018	0.198*	−0.583*	1

Abbreviations: ALS-FRS-R, revised Amyotrophic Lateral Sclerosis Functional Rating Scale; AMS, average minimum saturations; FVC%, forced vital capacity; HCO_3^-, carbonate; MPS, mean oxygen percentage saturation; ODI, oxygen desaturation index; pCO_2, carbon dioxide; SBE, standard base excess; T90, percentage of recording time spent with oxygen saturation at <90%.

*$p<0.05$.

TABLE 3 Median FVC% values for different ranges of ABG and OvOx parameters of the Milan cohort.

ABG and OvOx measurements	FVC%, median value (IQR)	*p* value
pCO_2, mmHg		**<0.01**
<39	72.6 (55.0–95.0)	
39–42	71.9 (55.0–89.0)	0.86
42–45	62.8 (47.0–75.0)	0.15
>45	52.8 (38.0–63.8)	**0.03**
HCO_3^-, mmol/L		**<0.01**
<24	76.2 (59.8–98.0)	
24–26	72.3 (56.0–88.8)	0.58
26–28	66.6 (50.0–85.5)	0.85
>28	50.8 (36.0–60.0)	**<0.01**
SBE, mol/L		**<0.01**
<2	72.7 (56.5–91.0)	
2–4	61.7 (45.5–79.0)	**0.02**
>4	51.3 (36.3–60.0)	**0.02**
T90		
<5%	75.2 (58.0–95.0)	
>5%	68.8 (49.0–85.5)	**0.04**
MPS		
>91%	77.1 (58.0–96.0)	
<91%	61.6 (44.0–73.0)	**0.01**
ODI		
<5	71.3 (52.8–93.3)	
>5	73.3 (56.0–93.0)	0.72
AMS		
>88%	74.8 (56.0–95.0)	
<88%	63.5 (49.0–76.5)	**0.02**

Note: Comparison of FVC% values at different ABG or OvOx levels. To compare the variable of interest among multiple groups one-way analysis of variance was used. To compare the variable of interest between pairs of groups (each respiratory parameter range with the previous one) a Mann–Whitney *U* test was used. Bold values denote statistical significance.

Abbreviations: ABG, arterial blood gas; AMS, average minimum saturations; FVC%, forced vital capacity; HCO_3^-, carbonate; IQR, interquartile range; MPS, mean oxygen percentage saturation; ODI, oxygen desaturation index; OvOx, overnight oximetry; pCO_2, carbon dioxide; SBE, standard base excess; T90, percentage of recording time spent with oxygen saturation at <90%.

pCO_2 > 45 mmHg, SBE > 2 mmol/L and MPS <91%. The points for these six variables were then added together to arrive at a final score, with a maximum total of 8 points (Table 6). Univariate Cox regression analysis disclosed a significant HR for different categories of values assessed through the respiratory score (Mantel–Cox; $\chi^2 = 34.8$; 4–6 points: HR 2.2, 95% CI 1.4–3.4; 7–8 points: HR 4.2, 95% CI 2.5–6.9; $p < 0.05$ [Figure 1a]). Mean survival, measured through Kaplan–Meier analysis followed by log-rank test, stratified for prognostic subgroups according to the respiratory score values was as follows (Figure 1a; $p < 0.05$): score <3: 27.3 months (95% CI 19.4–35.2 months); score 4–6 points: 12.6 months (95% CI 9.6–15.6 months); score >6 points: 6.9 months (95% CI 4.1–9.8 months). Multivariate Cox regression analysis confirmed the independent effect of the respiratory score on survival and the increased HR for each subgroup of patients (Mantel–Cox; $\chi^2 = 50.3$; 4–6 points: HR 1.9, 95% CI 1.2–3.1; 7–8 points: HR 3.1, 95% CI 1.7–5.4; $p < 0.05$ [Figure 1b]). Similarly, mean time to NIMV adaptation was significantly different among each subgroup of patients with regard to respiratory score (0–3 points: 20.3 months, 95% CI 13.7–26.9; 4–6 points: 10.2 months, 95% CI 6.0–14.3; 7–8 points: 0.6 months, 95% CI 0.00–1.1; $p < 0.05$ [Figure 1c]).

We next replicated the prognostic role of the respiratory score on the independent Turin control cohort. Univariate Cox regression analysis confirmed the increased HR for the three subgroups of patients (Mantel–Cox; $\chi^2 = 62.9$; 4–6 points: HR 3.0, 95% CI 2.1–4.4; 7–8 points: HR 7.9, 95% CI 4.0–15.3; $p < 0.05$ [Figure 2a]). Moreover, multivariate Cox regression analysis confirmed the independent effect of respiratory score on survival (Mantel–Cox; $\chi^2 = 78.4$; 4–6 points: HR 2.4, 95% CI 1.5–3.7; 7–8 points: HR 4.9, 95% CI 2.2–10.9; $p < 0.05$ [Figure 2b]). Finally, Kaplan–Meier analysis showed a significant difference in mean time to NIMV adaptation among each subgroup of patients (0–3 points: 51.2 months, 95% CI 40.5–61.9; 4–6 points: 23.6 months, 95% CI 17.7–29.4; 7–8 points: 4.9 months, 95% CI 2.4–7.3 [Figure 2c]).

DISCUSSION

In this study, in two large cohorts of non-ventilated MND patients, we evaluated spirometric, ABG and OvOx variables and considered their prognostic role as single or combined parameters. Although current guidelines on the respiratory assessment of MND patients recommend that these RTs are regularly performed, and despite the fact that respiratory failure is one of the main causes of death in MND, to date, only few studies have evaluated their combined role in prognosis [3, 11, 13, 22]. Each of these tests are simple to perform, cheap, and non- or minimally invasive and allow the physician to explore different aspects of respiratory function, and have been shown to be indispensable and complementary to each other in the respiratory management of MND patients. Moreover, our study provides a simple score that can be used in clinical practice and may help to guide decisions on the timing of NIMV adaptation and on end-of-life care, and to better stratify patients in clinical trials.

Among respiratory parameters, HCO_3^- was determined to be the measurement that best correlated with ALS-FRS-R respiratory subscore, followed by pCO_2 and FVC. However, each of these parameters showed only moderate correlations with respiratory symptoms, reflecting their limited predictive power with regard to respiratory symptoms [14]. Moreover, ALS-FRS-R respiratory subscore was not correlated with MPS and ODI and was only poorly correlated with AMS and T90. This might be explained by the increased relevance of

TABLE 4 Median ABG values for different ranges of OvOx parameters of the Milan motor neuron disease cohort.

OvOx measurament	ABG analysis, median value (IQR), pCO_2	*p* value	ABG analysis, median value (IQR), HCO_3^-	*p* value	ABG analysis, median value (IQR), SBE	*p* value
T90						
<5%	41.4 (37.7-43.4)		26.2 (24.4-27.7)		1.8 (0.5-3.4)	
>5%	44.2 (40.2–48.1)	0.01	27.7 (25.6–29.4)	0.01	2.6 (1.2–4.4)	**0.04**
MPS						
<91%	44.5 (41.6–48.6)		27.8 (26.0–29.6)		2.9 (1.4–4.6)	
>91%	42.1 (38.0–44.2)	0.01	26.5 (24.5–28.5)	0.01	2.0 (0.5–3.5)	**0.04**
AMS						
>88%	41.7 (37.9–44.0)		26.5 (24.7–27.9)		1.9 (0.6–3.4)	
<88%	46.1 (42.2–49.8)	0.01	28.4 (25.8–30.2)	0.01	3.0 (1.2–5.2)	**0.04**

Note: Bold values denote statistical significance.

Abbreviations: ABG, arterial blood gas; AMS, average minimum saturations; FVC%, forced vital capacity; HCO_3^-, carbonate; IQR, interquartile range; MPS, mean oxygen percentage saturation; ODI, oxygen desaturation index; OvOx, overnight oximetry; pCO_2, carbon dioxide; SBE, standard base excess; T90, percentage of recording time spent with oxygen saturation at <90%.

TABLE 5 Respiratory measurements and survival of the Milan motor neuron disease cohort (univariate analysis).

Respiratory variable		Mean survival (months)	95% CI	HR	95% CI	*p* value
FVC%	>95%	62.9	48.0–77.7			
	95–76%	31.2	23.5–38.9	1.9	1.4–2.6	**<0.01**
	76–58%	23.3	19.0–27.6	2.5	1.9–3.4	**<0.01**
	<58%	14.5	11.0–17.9	4.2	3.1–5.8	**<0.01**
ΔFVC%	<2	42.6	35.8–49.4			
	>2	15.7	12.8–18.7	2.5	2.0–3.1	**<0.01**
pCO_2	<42 mmHg	21.4	16.5–26.3			
	42–45 mmHg	14.2	10.7–17.7	1.4	0.9–2.1	0.12
	>45 mmHg	13.1	9.0–17.1	1.6	1.1–2.3	**0.01**
HCO_3^-	<24 mmol/L	33.6	19.5–47.8			
	24–26 mmol/L	15.7	11.2–20.3	2.1	1.3–3.7	**<0.01**
	>26 mmol/L	14.9	12.1–17.7	2.3	1.4–3.7	**<0.01**
SBE	<2 mmol/L	20.8	16.3–25.3			
	>2 mmol/L	13.8	10.6–17.0	1.5	1.1–2.1	**0.01**
T90	<5%	26.2	20.4–31.9			
	>5%	18.3	14.0–22.6	1.3	0.9–1.7	0.11
MPS	>91%	25.3	20.5–30.0			
	<91%	16.9	10.7–23.2	1.5	1.0–2.1	**0.04**
AMS	<88%	19.1	12.8–25.6			
	>88%	25.2	20.2–30.3	0.8	0.5–1.2	0.28
ODI	>5	19.9	14.7–25.2			
	<5	25.0	19.7–30.4	0.8	0.6–1.2	0.34

Note: Bold values denote statistical significance.

Abbreviations: ABG, arterial blood gas; AMS, average minimum saturations; CI, confidence interval; FVC%, forced vital capacity; HCO_3^-, carbonate; HR, hazard ratio; MPS, mean oxygen percentage saturation; ODI, oxygen desaturation index; pCO_2, carbon dioxide; SBE, standard base excess; T90, percentage of recording time spent with oxygen saturation at <90%.

pCO_2, compared to pO_2, with regard to respiratory symptomatology. [23]

The Mann–Whitney *U* test revealed a severe reduction of FVC% when the majority of ABG and OvOx values showed respiratory impairment. It is notable that loss of motoneurons causes restrictive lung failure and consequently a progressive reduction of the FVC measurement. Moreover, when respiratory muscle weakness worsens and the FVC is markedly reduced, the tidal volume is also impaired, and the development

of complications, such as atelectasis, increases; these events further worsen pulmonary shunts, leading to hypercapnia and hypoxemia [5, 24]. Interestingly, we noticed that levels of pCO_2, HCO_3^- and SBE were close to reference limits when compared with normal OvOx values, whereas they were markedly increased when compared with OvOx values that were close to the reference limits or revealing slight functional impairment (ie, T90 is >5%, MPS is <91% and AMS is <88%). This observation supports the notion that nocturnal hypoxemia due to NH is usually a late finding in neuromuscular disorders and happens when chemoreceptors are tailored to increased levels of pCO_2 [25]. However, nocturnal hypoxemia may also be promoted by sleep apneas, which are a common finding during the MND disease course [14]. We did not observe differences in FVC% or ABG measurements (data not shown) for different groups of ODI values and our results highlight the importance of performing OvOx in MND patients to detect sleep apnea since sleep apnea entails the need of accurate titration of ventilator settings [14, 15, 26, 27].

TABLE 6 The Milan-Torin respiratory score (Mi-To-RS).

Respiratory test	Parameter	Cut-off	Points
Spirometry (0–4 points)	FVC%	>95%	0
		Between 95% and 76%	1
		Between 75% and 60%	2
		<59%	3
	ΔFVC%	<2	0
		>2	1
ABG (0–3 points)	HCO_3^-	<26 mmol/L	0
		>26 mmol/L	1
	pCO_2	<45 mmHg	0
		>45 mmHg	1
	SBE	<2 mmol/L	0
		>2 mmol/L	1
OvOx (0–1 points)	MPS	>91%	0
		<91%	1
Total			8

Abbreviations: ABG, arterial blood gas; FVC%, forced vital capacity; HCO_3^-, carbonate; MPS, mean oxygen percentage saturation; OvOx, overnight oximetry; pCO_2, carbon dioxide; SBE, standard base excess.

Cox univariate analysis of FVC% confirmed that this measure is a strong predictor of survival [28], even when it is considered as ΔFVC%. In the Milan MND cohort, Cox univariate analysis of individual ABG parameters showed a significantly increased HR, and consequentially a shorter survival time in MND patients, when pCO_2 was >45 mmHg, HCO_3^- was >24 mmol/L and SBE was >2 mmol/L, confirming the prognostic role of ABG parameters [13, 29]. Interestingly, when considering ABG measurements individually, HCO_3^- was found to be the measurement with the earliest changes associated with a worse prognosis, being a negative prognostic factor when it increased above 24 mmHg, which is widely considered within reference limit values. This suggests that a mild increase in HCO_3^- might be an early

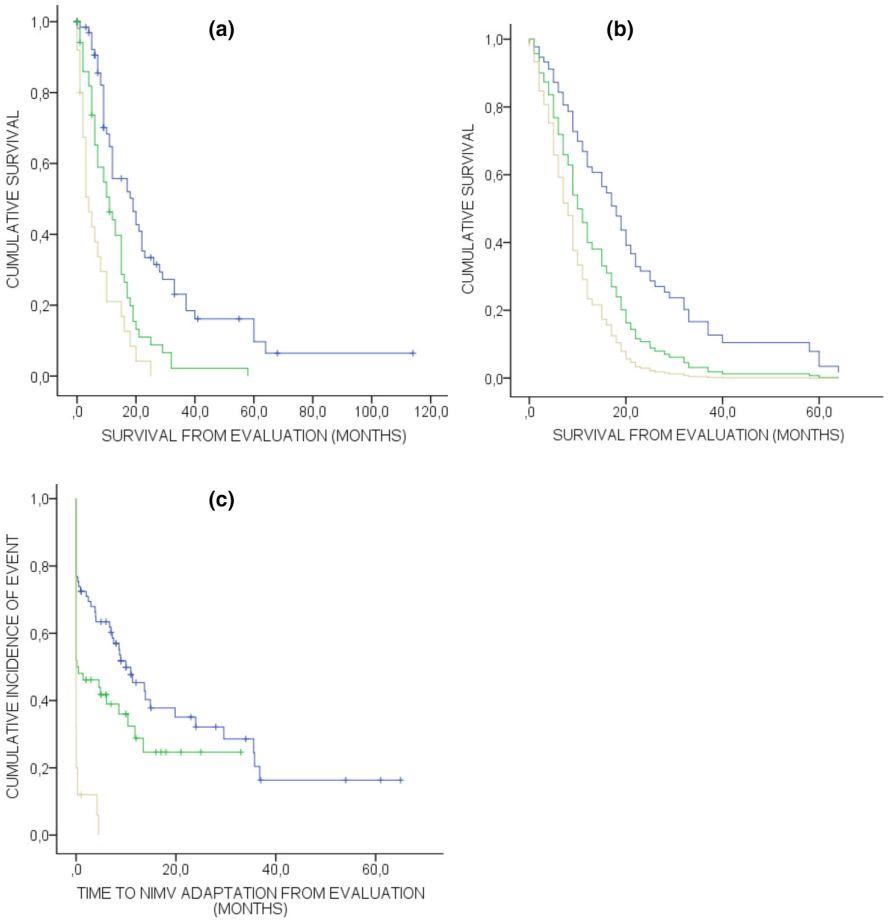

FIGURE 1 (a) Kaplan–Meier survival curves of the Milan motor neuron disease (MND) cohort grouped according to Milan-Torin respiratory score (Mi-To-RS). (b) Cox multivariate survival curves of the Milan MND cohort, adjusted for age at onset, site of onset, diagnostic certainty according to revised El Escorial criteria, change in revised Amyotrophic Lateral Sclerosis Functional Rating Scale, dementia and diagnostic delay (Table S2). Curves are grouped according to Mi-To-RS. (c) Kaplan–Meier curves describing time to non-invasive mechanical ventilation (NIMV) adaptation of the Milan MND cohort, grouped according to Mi-To-RS. Curves are grouped according to the proposed respiratory score: patients with 0–3 (blue line), 4–6 (green line) or 7–8 (yellow line).

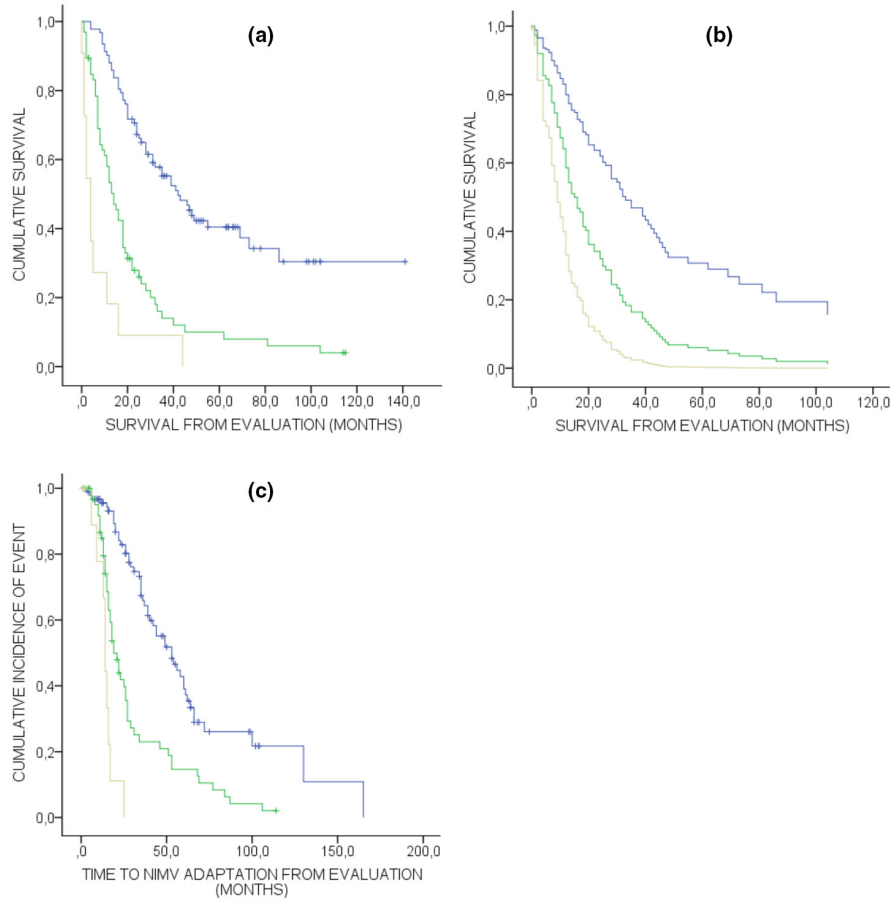

FIGURE 2 (a) Kaplan–Meier survival curves of the Torin motor neuron disease (MND) cohort grouped according to Milan-Torin respiratory score (Mi-To-RS). (b) Cox multivariate survival curves of the Torin MND cohort, adjusted for age at onset, site of onset, diagnostic certainty according to revised El Escorial criteria, change in revised Amyotrophic Lateral Sclerosis Functional Rating Scale, dementia and diagnostic delay (Table S3). Curves are grouped according to Mi-To-RS. (c) Kaplan–Meier curves describing time to non-invasive mechanical ventilation (NIMV) adaptation of the Torin MND cohort grouped according to the Mi-To-RS. Curves are grouped according to the proposed respiratory score: patients with 0–3 (blue line), 4–6 (green line) or 7–8 (yellow line).

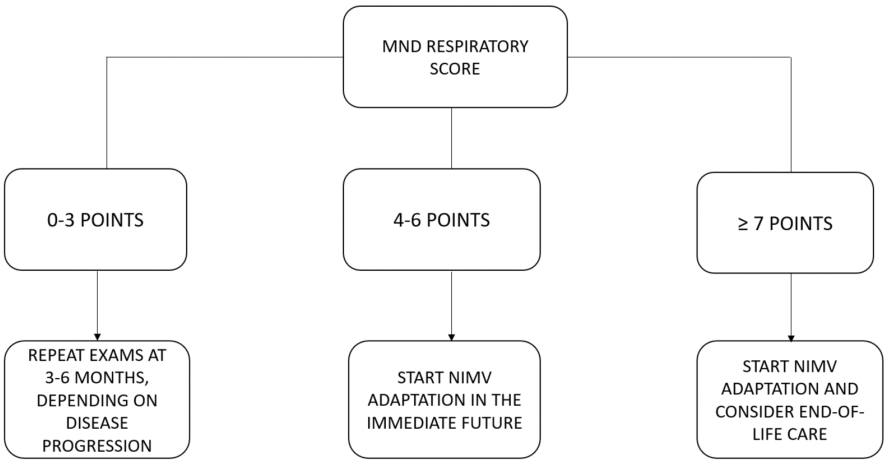

FIGURE 3 Diagnostic and therapeutic algorithm of the respiratory management according to the proposed respiratory score. MND, motor neuron disease; NIMV, non-invasive mechanical ventilation.

indicator of NH or that it might also be influenced by the time at which ABG is performed during the day. Among the OvOx variables, only MPS (settled at the cut-off of 91%) was significantly associated with survival. Notably, only a single previous report in a limited cohort of MND patients addressed the prognostic role of OvOx, reporting shorter survival in patients with an MPS value <93% [30]. Nevertheless, both these values (93% and 91%) are very close to each other in the plateau of the oxygen/hemoglobin dissociation curve and correspond to similar values of pO_2. The drop of MPS measurement in the 93%–91% range might be considered an additional threshold for OvOx abnormalities and may precede NH or respiratory failure development, resulting in shorter survival [6]. Moreover, since sleep apneas often accompany NH, they may have contributed to reducing the MPS value, concurring with the poorer prognosis [14, 15, 27].

PROGNOSTIC SCORE

The combination of the six independent respiratory function predictors (i.e., FVC%, ΔFVC%, pCO_2, HCO_3^-, SBE and MPS) resulted

in a prognostic score significantly associated with survival. Three different risk groups were identified according to the presence of 0–3, 4–6, or >6 points, respectively ($p < 0.05$ [Figures 2 and 3]). Interestingly, when a patient exceeded the cut-off of 4 points, this corresponded to a significantly decrease in survival and time to NIMV initiation. This score might be the result of a severe reduction of FVC%, together with an increased ΔFVC%, a moderate or slight reduction of FVC%, together with an increased ΔFVC%, and/or ABG and/or OvOx abnormalities. However, each of these situations is associated with an early development of respiratory symptoms, and justifies NIMV adaption in the immediate future (Figure 3). [3, 11, 13, 14, 31]

To the best of our knowledge, this is the first study to evaluate the combined role of three respiratory parameters in a large cohort of non-ventilated MND patients and is the first to create a respiratory score that may be useful in both the management and to predict the prognosis of MND patients. However, we acknowledge that this study has some limitations. First, the criteria used for our cohort selection may have led to the exclusion of patients unable to perform the spirometry, such as patients with bulbar onset and facial muscle weakness. Moreover, ABG and OvOx data were not available for all patients. However, our cohort included an acceptable number of bulbar patients and although, in the initial population, only 40% of patients had ABG and only 55% had OvOx measurements, the main difference among patients for whom ABG and OvOx data were available compared with the total cohort was a higher disease progression rate, which may have led the clinician to complete the respiratory assessment with these two RTs (Table S4). Nevertheless, our results were replicated in an independent cohort of patients, for whom all the respiratory measurements were available, confirming the association of the score with outcome in both bulbar and spinal patients (Figure S2). Lastly, we did not evaluate other respiratory measurements such as maximal inspiratory/expiratory pressure, sniff nasal inspiratory pressure or parameters of transcutaneous capnography or polysomnographic tests, however, the RTs recommended by current guidelines to evaluate the need for NIMV adaptation are currently represented by spirometry, ABG and OvOx [3]. Second, the Kaplan–Meier analysis in the Turin cohort confirmed the prognostic role of the respiratory score but led to a degree of variability in the quantification of mean survival or time to NIMV adaptation for each considered subgroup according to the proposed score. The difference in survival times between the two cohorts might be explained by different patient selection and by the different rate of patients who underwent NIMV adaptation, although no significant difference emerged from analysis comparing the main clinical features of the two cohorts (Table S5). Third, this was a retrospective study; for this reason, the presence of respiratory symptoms could be investigated only through the ALS-FRS-R score, and we could not include longitudinal data on ALS-FRS-R or respiratory measurements. Fourth, RTs were performed at a different time during the disease course of each patient and it has been shown that the rate of decline of FVC% might not be linear, leading to a degree of interpatient variability [32]. Moreover, we calculated ΔFVC% based on the assumption that the premorbid FVC% was 100%, but longitudinal assessment may allow better estimation of this parameter. Finally, the results of genetic analysis were not available for the majority of the cohort, leading us to exclude these variables from the Cox regression model.

In summary, we demonstrate that FVC%, ABG and OvOx measurements provide different and complementary information in the respiratory management and prognosis of MND patients. The combination of these variables into a single score might help the neurologist to predict prognosis and to correctly stratify patients in clinical trials. Moreover, the use of this score might facilitate the respiratory management of such patients and to guide different types of diagnostic or therapeutic approach (Figure 3). Further studies are needed to assess the independent role of these respiratory variables in each MND phenotype and the clinical relevance of the proposed prognostic score.

CONFLICT OF INTEREST STATEMENT

All authors declare that they have no conflicts of interest related to this paper.

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 at the end of this article.

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