Journal of Critical Care 50 (2019) 54–58

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Survival of amyotrophic lateral sclerosis patients after admission to the intensive care unit for acute respiratory failure: an observational cohort study

Julien Mayaux [a,f], Jérôme Lambert [b,c], Capucine Morélot-Panzini [a,d], Jésus Gonzalez-Bermejo [a,d], Julie Delemazure [a], Claudia Llontop [a], Gaëlle Bruneteau [f], François Salachas [e], Martin Dres [a,d], Alexandre Demoule [a,d], Thomas Similowski [a,d,*]

[a] AP-HP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Service de Pneumologie, Médecine Intensive et Réanimation, Département "R3S", F-75013 Paris, France
[b] AP-HP, Hôpital Saint-Louis, Département de Biostatistiques et Informatique Médicale, F-75010 Paris, France
[c] INSERM, UMRS 717, Paris, France
[d] Sorbonne Université, INSERM, UMRS1158 Neurophysiologie respiratoire expérimentale et clinique, F-75005 Paris, France
[e] APHP, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, Département de Neurologie, Centre Référent SLA, F-75013 Paris, France
[f] Sorbonne Université, Institut du Cerveau et de la Moelle épinière, ICM, Inserm U 1127, CNRS UMR 7225, F-75013 Paris, France

ARTICLE INFO

Keywords:
Amyotrophic lateral sclerosis
Acute respiratory failure
Intensive care unit
Chronic respiratory failure

ABSTRACT

Purpose: Amyotrophic lateral sclerosis (ALS) entails a risk of acute respiratory failure (ARF). The decision to admit such patients to the intensive care unit (ICU) is difficult given the inexorable prognosis of ALS. To fuel this discussion, this study describes the ICU and post-ICU survival of ALS-related ARF.
Material and methods: Retrospective cohort analysis over 10 years (university hospital setting, ALS reference center).
Results: Of 90 patients (66 men, median age: 67 [IQR 59–71], median interval since ALS diagnosis: 26.5 months [14–53], ALSFRS-R: 19 [12—30], bulbar signs 73%), 48 were managed by noninvasive ventilation (NIV) only, 7 were already tracheotomized upon admission, 12 were tracheotomized during the ICU stay (advance care planning project), 18 were already intubated before admission, 5 received oxygen and physiotherapy only. Median ICU stay was 4 days [2-9] with 20% mortality. Median hospital stay was 10 days [5–22] with 33% mortality. The 3-month and one year mortality wer 46% and 71%. Hospital mortality was higher in patients with more severe respiratory acidosis and higher simplified acute physiology scores on admission.
Conclusions: The prognosis of ALS-related ARF requiring ICU admission resembles that of ARF complicating other conditions with high short-term mortality (e.g. lung cancer).

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1. Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder of unknown origin that results in muscle wasting. Respiratory muscle involvement leads to chronic respiratory failure, which is a prominent cause of ALS-related deaths. In this context, home noninvasive ventilation (NIV) has become a standard of care in ALS: it alleviates dyspnea, improves sleep and quality of life, and prolongs survival [1,2]. There is no curative treatment for ALS, although riluzole has been shown to prolong survival and edaravone to slow down disease progression. Clinical and functional deterioration is generally curvilinear over time [3]: ALS is generally fatal within the 2 to 5 years that follow the onset of symptoms, but there are long survivors of which the number might be increasing as a result of the generalization of multidisciplinary care.

Episodes of acute respiratory failure are common during the course of ALS, consequences of pneumonia and atelectasis resulting from cough and swallowing impairment [4] or from pulmonary embolisms that are also frequent [5]. These episodes, occurring in patients with underlying altered respiratory function, can be life-threatening and raise the question of intensive care unit (ICU) admission. As in other diseases characterized by a very severe prognosis, the decision to admit ALS patients to the ICU is often considered particularly difficult given the inexorable underlying prognosis. Although this has not been precisely documented in the literature, clinical experience suggests that the ICU admission of ALS patients is often censored (namely either not proposed by the clinicians in charge of the patients or refused by intensivists) based on a preconceived notion of futility. The aim of the

* Corresponding author at: Service de Pneumologie, Médecine Intensive et Réanimation, Groupe Hospitalier Pitié-Salpêtrière Charles Foix, 47–83 Bd de l'Hôpital, 75, 651, Paris, Cedex 13, France.
E-mail address: thomas.similowski@psl.ap-hop-paris.fr (T. Similowski).

https://doi.org/10.1016/j.jcrc.2018.11.007
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present study was therefore to provide data on the survival of ALS patients admitted to a medical ICU for acute respiratory failure and the corresponding prognostic factors, with particular emphasis on noninvasive ventilation.

2. Material and methods

2.1. Setting

This study was based on retrospective analysis of data prospectively collected in an institutional database. The database describes the activity of a 16-bed medical ICU situated in a in a 1700-bed university hospital and that belongs to a department of respiratory and intensive care medicine that specializes in the care of patients with various forms of chronic respiratory insufficiency. This department constitutes the "respiratory branch" of the local reference centre for ALS. The study was conducted over a 10 years period, during which about 3500 ALS patients followed by the ALS reference centre were admitted to the hospital at least once (of note, at any given time the ALS reference centre manages about 800 patients, as a result of the respective fluxes of new diagnosis and deaths; the respiratory branch of the centre currently follows-up a cohort of about 500 ALS patients under home mechanical ventilation -noninvasive ventilation, NIV, in more than 95% of cases-; the size of this cohort has been increasing steeply over the first 5 years of the study and has stabilised since). The present study was approved by the ethics committee of the French learned society for intensive care medicine (*Société de Réanimation de Langue Française*).

2.2. Inclusion and exclusion criteria

The patients were included in the analysis if: 1) diagnosis of definite or probable ALS according to the revised "El Escorial" criteria [6]; 2) acute respiratory failure, defined by a respiratory rate of 30/min or more, associated with signs of increased work of breathing, or PaO_2 less than 60 mmHg on room air, or initiation of ventilatory assistance prior to admission; 3) first ever admission to an ICU. Repeated stays (second or more) in a given patient were excluded from the analysis, as well as stays justified by monitoring of a scheduled procedure (feeding gastrostomy or tracheotomy placement).

2.3. Source and type of data analyzed

The data analyzed were extracted from the intensive care unit's prospective database for data concerning ICU stays and from the national database of patients with ALS and related syndromes for data concerning the disease. Medical records were reviewed whenever necessary.

The following data were extracted:

- age and gender;
- description of the neurological disease: history (interval between diagnosis of ALS and ICU admission), clinical evaluation during the 3 months before admission (presence of clinical signs of bulbar involvement -yes vs. no-, ALSFRS-R, muscle testing, ability to walk -yes vs.no-);
- description of respiratory impairment before admission: home ventilation (modalities, interval between initiation of home ventilation and ICU admission), vital capacity during the previous 3 months for patients not ventilated at home and at the time of initiation of ventilation in the other patients; oxygen therapy;
- description of the intensive care unit stay: exact reason for admission, laboratory data on day 1, severity scores (Simplified Acute Physiological Score 2 – SAPS II – and Sepsis-related Organ Failure Assessment – SOFA) on day 1, presence or absence of ventilatory assistance during the stay and, in the presence or ventilatory assistance, type of interface (NIV or intubation) and duration (interface and duration); possible decision to withhold care; survival;
- description of the hospital stay (duration; mode of discharge - death or survival; return home);
- 3-month survival after the hospital stay.

2.4. Statistical analysis

Statistical analysis was conducted with R software v2.10.1 (http://www.r-project.org). Categorical data are expressed as number of events and percentages and compared by Fisher's exact test. Quantitative variables are expressed as the median (interquartile range) and compared by a Wilcoxon's test. Survival curves were plotted by the Kaplan-Meier method and, when applicable, were compared by a log-rank test. Risk factors for 3-month mortality were determined by univariate analysis followed by multivariate analysis (but no multivariate model was found to be significant).

Statistical analysis was conducted on the entire cohort identified from the database. Comparisons for the risk of in-hospital mortality were performed using a Fine and Gray competitive risk model [7]. Finally, as changes in clinical practice inevitably occurred during the period of interest, a comparison on the primary endpoint – 3-month survival - was conducted between the first and second halves of the 10 year period. As no significant difference was demonstrated, data for the entire period were analyzed. The limit of significance was defined as a p value less than or equal to 0.05.

3. Results

Ninety patients were included in the study. They presented a median SAPS II score of 28 [24–35] and a median SOFA score of 3 [3]. The median $PaCO_2$ on admission was 47 mmHg [41–60], with a median pH of 7.40 [7.34–7.44]. The reasons for admission and the final diagnoses adopted were decompensation of underlying chronic respiratory failure due to congestion, atelectasis, pneumonia or probable aspiration ($n = 82$, 91.1%), pulmonary embolism ($n = 4$, 4.4%), cardiorespiratory arrest ($n = 2$, 2.2%), abdominal emergency (n = 2, 2.2%). At the time of ICU admission, 73% had signs of bulbar involvement ranging from mild to severe, 46% were tetraparetic or tetraplegic and 42% were still able to walk. The mean ALSFRS-R score was 19 [12–30], corresponding to severe disability. Thirty-three patients (37%) were on home ventilatory support (NIV: $n = 26$, only at night in 13 patients; tracheotomy: $n = 7$), which had been initiated 6 months [1.5–12.5] before the acute episode. Mean vital capacity (last documented value) was 45% of predicted. Mean $PaCO_2$ upon admission was 49 mmHg.

Eighteen patients were admitted to the ICU already intubated, either in another ICU or during pre-hospital management. Twelve of these patients were extubated during the stay, but were immediately placed on post-extubation NIV, 4 patients died without being extubated, 1 patient was extubated and did not require post-extubation NIV, and 1 patient was transferred to another department after staying in the ICU for 24 h without being extubated. Seven patients had already been tracheotomized at the time of ICU admission. Twelve patients were tracheotomized during the ICU stay, while on NIV (all of them during the first two years of the observation period). These tracheotomies were all performed in the context of a defined care project prior to the acute episode, and corresponded to the wishes clearly expressed by the patients and repeated during the ICU stay. Although this was not a constant pattern, the patients who opted for a tracheotomy were generally younger, had young children, or had a predominantly respiratory form of the disease with preserved mobility. Forty-eight patients were managed exclusively by NIV. Five patients only required oxygen therapy and intensive decongestion. The ICU stay lasted 24 h in 4 of these cases and 48 h in 5th case.

The median length of ICU stay was 4 [2-9] days, with 20% mortality (18 deaths). The median length of hospital stay was 10 [5–22] days with 33% mortality (30 deaths). Factors associated with in-hospital mortality are described in Table 1, noting that none of the multivariate models was significant. The three-month mortality was 48% (43 deaths) and the one-year mortality was 71% (66 deaths). Table 2 compares the surviving and deceased patients at 3 months. Only age and the degree of respiratory acidosis upon admission (namely the severity of hypoventilation) differed between the two categories of patients. Overall, the median survival following ICU admission was 118 days (Fig. 1). Tracheotomy was associated with a survival advantage (log-rank test; $p = .02$) but there was no difference between the various others types of management of ventilatory assistance (including for the 48 patients managed exclusively by NIV).

4. Discussion

4.1. ICU mortality

In this population of ARF patients with advanced ALS, ICU mortality was 20% and hospital mortality 33%, a severe prognosis. The ICU mortality was much higher than the 4–5% predicted (and otherwise observed in the unit) on the basis of the SAPS 2 score [8], suggesting ALS-specific features. For example and as per unit policy, life-supporting treatments other than mechanical ventilation were withheld if multivisceral failure developed, the ICU project then taking a palliative orientation. Nevertheless, 48% of patients were alive at 3 months and 29% were alive at one year, figures that have to be put in the perspective of the general prognosis of ALS. Likewise, about one third of our patients had been on home mechanical ventilation for an average of 6 months prior to their ICU admission which, in our experience, corresponds to a life expectancy of about a year [9-11]. Of note, similar or worse post-ICU survival has been described in other situations. In allogeneic bone marrow transplant recipients, ICU mortality can reach 65% [12-14] with a 1-year mortality over 75%. In patients with lung cancer (all types and all stages), an

Table 1
Risk of in-hospital mortality.

	SHR	95%CI	p value
Demographic characteristics			
Age	1.02	[0.97–1.07]	0.53
Gender	1.21	[0.47–3.07]	0.69
Description of ALS			
Time from diagnosis upon ICU admission	1.01	[1.00–1.01]	***0.01***
ALSFRS-R score	1.01	[0.96–1.06]	0.67
Bulbar involvement	0.95	[0.40–2.25]	0.92
Tetraplegia	1.97	[0.85–4.55]	0.11
Walking	0.49	[0.20–1.24]	0.13
ALS-related chronic respiratory insufficiency			
Home mechanical ventilation	1.10	[0.47–2.53]	0.83
Interval between initiation of home ventilation and ICU admission	1.01	[0.97–1.05]	0.70
Severity upon ICU admission			
$PaCO_2$	1.03	[1.00–1.06]	***0.04***
pH	0.01	[0–0.04]	***0.01***
SAPS II	1.03	[1.00–1.06]	***0.02***
SOFA	1.27	[0.71–2.27]	0.4
ICU and hospital stay			
Median length of ICU stay	0.97	[0.90–1.04]	0.48
Median length of hospital stay	0.91	[0.85–0.98]	***0.02***

SHR, sub-hazard ratio. CI: confidence interval; ALS, amyotrophic lateral sclerosis; ICU, intensive care unit; ALSFRS-R, ALS functional rating scale, revised; SAPS II, simplified acute physiology score, version II; SOFA: sepsis-related organ failure assesment.

Table 2
Univariate comparison of deceased and surviving patients 3 months after ICU admission.

	Dead at 3 months	Alive at 3 months	p
Number of patients	43 (49%)	44 (51%)	
Demographic characteristics			
Age (years)	69 [63–74]	63 [58–69.5]	***0.01***
Male gender	28 (65%)	36 (82%)	0.09
Description of ALS			
Time from diagnosis upon ICU admission	31 [15–63]	27 [14–45]	0.43
ALSFRS-R score	19 [15–30]	19 [10−30]	0.80
Bulbar involvement	30 (73%)	32 (73%)	1
Muscle testing	79 [48–112]	93 [72–133]	0.22
Tetraplegia	22 (51%)	19 (43%)	0.52
Walking	14 (34%)	20 (46%)	0.37
ALS-related chronic respiratory insufficiency			
Vital capacity (% predicted))	43% [41–49]	49% [40–61]	0.36
Home ventilation	30 (70%)	25 (57%)	0.15
Interval between initiation of home ventilation and ICU admission (months)	8 [1–19]	5 [3–28]	0.73
Severity upon ICU admission			
pH on day 1	7.37 [7.32–7.42]	7.42 [7.38–7.44]	***0.004***
$PaCO_2$ on day 1 (mmHg)	50 [44–66]	44 [37–58]	***0.01***
SAPS II	30 [27–37]	27 [24–32]	0.08
SOFA	3 [3–3]	3 [3–3]	0.73
Management of ventilatory assistance during the ICU stay			
NIV only	24 (56%)	22 (50%)	0.66
Post-extubation NIV	6 (14%)	6 (14%)	0.97
Tracheotomy	5 (11%)	13 (30%)	0.06
Initiation of home ventilation in ICU	15 (35%)	16 (36%)	1
ICU and hospital stay			
Median length of ICU stay (days)	3 [1−10]	4 [2–8]	0.47
Median length of hospital stay (days)	9 [3–15]	13 [6–22]	0.06

Values are provided as "number (percentage)" or "median [interquartile range].
ICU, intensive care unit; ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS functional rating scale, revisded; SAPS II, simplified acute physiology score, version II; SOFA, sepsis-related organe failure assessment; NIV, non-invasive ventilation.
(*) Three patients were lost to follow-up. This analysis therefore pertains to 87 of the 90 patients of the cohort. Results expressed as numbers with percentage, or median and interquartile range. Qualitative variables were compared by Fisher's exact test, quantitative variables were compared by Wilcoxon's test.

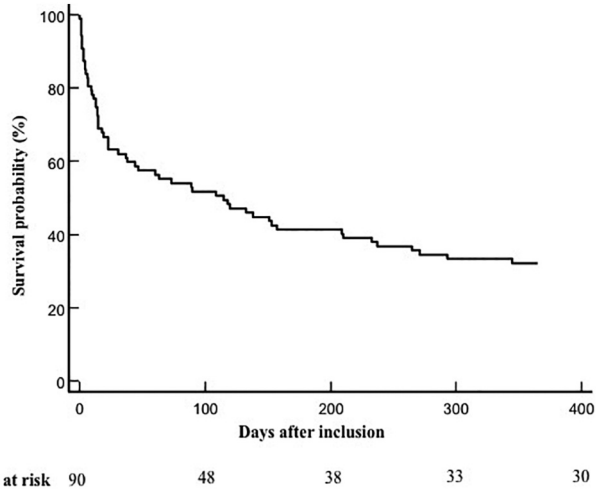

Fig. 1. Survival curve for the overall cohort established by the Kaplan-Meier method, truncated at one year.

international multicenter study reported an ICU mortality of 28%, a 3-month mortality of 39%, and a 6-month mortality of 55% [15].

4.2. Prognostic factors

Table 1 shows that only the disease duration prior to the ICU admission, the severity of hypoventilation and the SAPS 2 score were predictive of hospital mortality. The SOFA score and the ALSFRS-R scores were not predictive, probably because of a very narrow distributions. Bulbar involvement was also not predictive, which may appear surprising in view of the difficulties of NIV in this setting [16,17] but however consistent with recent data obtained in the home mechanical ventilation context [18]. The analysis was performed by considering "bulbar involvement" as a dichotomous variable without taking a severity into account: it is possible that some of the "bulbar" patients included in this study had an involvement moderate enough not to compromise the efficacy of NIV. From our study alone, bulbar involvement should not suffice to preclude ICU admission for ARF. However, common sense would suggest caution in bulbar patients in whom home NIV has already proven impossible. A tracheotomy already present upon ICU admission was associated with low mortality. This is expected in a context of isolated acute respiratory failure and corresponds to published data [19]. A preexisting tracheotomy should thus not preclude ICU admission, particularly if the tracheotomy is part of an advance care planning project. Of note, this was the case in all our patients; no emergency tracheotomy was performed.

Table 2 shows that age and the severity of hypoventilation on ICU admission are the only factors associated with higher 3-month mortality.

4.3. Strengths and limitations

Few data describe survival in ALS patients after an acute respiratory episode. The study of Pisa et al. [20], showing that acute respiratory episode markedly deteriorate prognosis, did not pertain to ICU admissions. The study of Vianello et al. [19] focused on tracheotomized patients only. Pertaining to a reasonably large population of patients, our study would therefore appear to be the first to specifically assess the outcome of ALS patients presenting an acute respiratory failure severe enough to be admitted to the ICU. This is an important strength, because the information brought about by the study is novel.

We are aware that our study has limitations that prevent considering it conclusive in any way. Firstly, this was a single-center, retrospective study, limited to ICU admissions for acute respiratory failure: this restricts the generalizability of the results. Secondly, the patients in our study were followed in a highly specialized ALS center characterized by efficient multidisciplinary care [21] and a long-standing close collaboration between neurologists, respiratory physicians and intensivists: this might constitute a positive bias regarding ICU indications (e.g. in terms of timing) and post-ICU survival. Indeed we believe that tight interactions between multidisciplinary care, ICU and palliative care are liable to considerably reduce the number of unwanted ICU admissions. Thirdly, we provide survival data but they should ideally have come with quality of life data (in the patients and their caregivers) that we do not have. Lastly, and perhaps most importantly, our study does not provide any data regarding the patients with ALS-related ARF who were not admitted to the ICU during the period of interest. We do not know their number, we cannot describe the mechanisms that led to the decision of non-admission, and we do not know how they were managed (e.g. palliative care) and what was their outcome. Nevertheless, we believe that our data provide a good rationale to design larger and prospective studies that would address the above issues. Such studies should aim at identifying criteria that can both avoid loss of chance and "futile" ICU admissions, both in terms of survival and in terms of quality of life. They should also aim at clarifying the ICU vs. palliative care decisional process, taking into account that the two can at times be strongly interdependent.

Acknowledgements

The author are grateful to Mr. Anthony Saul for the translation of the manuscript to English.

Funding details

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of interest

All the authors declare that their participation to this study did not involve any conflict of interest, financial or otherwise.

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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