Received: 17 May 2023 | Revised: 10 November 2023 | Accepted: 13 November 2023

https://doi.org/10.1016/j.rpth.2023.102287

ORIGINAL ARTICLE

Venous thromboembolism and amyotrophic lateral sclerosis: the Venous Thrombo-Embolism and Sclerosis Lateral Amyotrophic study

Audrey Barnabe[1] | Steeve Genestet[2] | Christophe Gut-Gobert[1,3] | Chloé Rivalain[1,3] | Jean-Baptiste Noury[2] | Marion Goret[1] | Aude Barnier[1] | Claire De Moreuil[1,3] | Benjamin Espinasse[1,3] | Raphaël Le Mao[1,3,4] | Christophe Leroyer[1,3,4] | Francis Couturaud[1,3,4] | Cécile Tromeur[1,3,4]

[1]Department of Internal, Vascular and Chest Diseases, Brest University Hospital, Brest, France

[2]Department of Clinical Neurophysiology, Brest University Hospital, Brest, France

[3]Unités mixtes de recherche 1304 Groupe d'Etude de Thrombose de Bretagne Occidentale, CIC-INSERM 1412, Univ_Brest, Brest, France

[4]French Clinical Research Infrastruture Network Investigation Network On Venous Thrombo-Embolism Network, Saint-Etienne, France

Correspondence
Cécile Tromeur, Département de Médecine Interne, Vasculaire et Pneumologie, Hôpital de la Cavale Blanche, Centre hopspitalier regional universitaire de Brest, 29609 Brest Cedex, France.
Email: cecile.tromeur@chu-brest.fr

Handling Editor: Dr Mary Cushman

Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a severe neurodegenerative disease. Given the inflammatory nature of ALS and the high number of ALS-related clinical circumstances (eg, prolonged immobilization and infections), patients with ALS may have a high risk of venous thromboembolism (VTE).

Objectives: To determine the annual incidence rate of VTE and the predictors of VTE in patients with ALS.

Methods: We analyzed a prospective cohort of patients with ALS diagnosed between 2009 and 2019 followed in the Brest University Hospital ALS Centre.

Results: Among 227 patients with ALS, VTE occurred in 19 patients during a median follow-up period of 717 days (IQR, 488-1308), yielding an annual incidence rate of 2.93% (95% CI, 1.88%-4.53%). Predictors for VTE were a family history of VTE (hazard ratio [HR], 15.24; 95% CI, 1.72-134.84; P = .01), the presence of noninvasive ventilation at ALS diagnosis (HR, 6.98; 95% CI, 1.09-44.59; P = .04) and a short time (ie, <213 days) between first symptoms and ALS diagnosis (HR, 5.48; 95% CI, 1.57-19.11; P = .01). Recurrent VTE occurred within 3 months after stopping anticoagulation in 5 patients (26.3%).

Conclusion: The annual incidence of VTE in patients with ALS is high. Predictive factors of VTE were a VTE history, noninvasive ventilation, and a short time between first symptoms of ALS and ALS diagnosis.

KEYWORDS
amyotrophic lateral sclerosis, anticoagulant, neurodegenerative diseases, pulmonary embolism, venous thromboembolism

Essentials

- Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease with no curative treatment.
- We studied the risk of venous thromboembolism (VTE) in ALS.
- The rate of VTE is high in patients with ALS, with a high rate of recurrence.
- Family history of VTE, ventilation, and short time to ALS diagnosis are risk factors for VTE.

1 | INTRODUCTION

Venous thromboembolism (VTE), including pulmonary embolism (PE) and deep vein thrombosis (DVT), is a frequent (1.83 cases per 1000 habitants per year) and potentially fatal disease [1]. In about 50% of cases, VTE occurs in the absence of clinical risk factors (ie, termed unprovoked VTE).

Amyotrophic lateral sclerosis (ALS) or Charcot's disease is a rare and serious neurodegenerative disease with poor survival (3-5 years after diagnosis) [2,3]. The mean time between the first symptoms and diagnosis ranges between 7 and 22 months [4,5]. ALS is characterized by damage to the upper and lower motor neurons, leading to progressive muscular paralysis until death. Despite the unavoidable immobilization, ALS is not usually recognized as a risk factor for VTE. In 2 retrospective studies, the annual incidence of VTE in patients with ALS ranged from 3% to 5% [6,7]. In a prospective study, VTE occurred in 11% of cases, 50% being asymptomatic [8], and muscular weakness was associated with an increased risk of VTE (P = .03). Recently, in a large prospective cohort of patients with VTE, after anticoagulation discontinuation, ALS was also found to be associated with an increased risk of recurrent VTE, reinforcing the hypothesis that ALS is probably associated with VTE [9]. Other studies also showed that VTE has an impact on morbidity and mortality in patients with ALS, with a mortality rate ranging from 2% to 6% [10,11]. However, large prospective cohorts are lacking regarding VTE incidence and risk factors of VTE in patients with ALS.

In a prospective study on patients with ALS, the primary aim was to determine the annual incidence rate of VTE. Secondary aims were to determine risk factors for VTE, the impact on survival, and the risk of recurrent VTE.

2 | METHODS

2.1 | Study design and population

The Venous Thrombo-Embolism and Sclerosis Lateral Amyotrophic (TESLA) study is a prospective cohort including patients with ALS followed in the ALS center in Brest University Hospital from January 2009 to December 2019. The protocol has been approved by the local ethical committee (29BRC19.0236) and recorded in clinicaltrials.gov (NCT04446325). All patients included received an information letter. In addition, patients with ALS who developed acute symptomatic VTE were prospectively included in the VTE prospective cohort of Brest University Hospital; the design and methods of this cohort have been previously published [9], and all patients with VTE provided written informed consent.

Inclusion criteria were as follows: (i) age of ≥18 years, (ii) patients with a likely or certain diagnosis of ALS according to the revised El Escorial criteria [12], and (iii) patients followed in the ALS center of Brest University Hospital. Exclusion criteria were refusal to participate, under legal protection, and neuromuscular diseases other than ALS (ie, myasthenia and Charcot–Marie–Tooth disease).

2.2 | Outcomes

The primary outcome was the occurrence of symptomatic VTE, including PE and/or isolated DVT. The diagnosis of VTE was confirmed using objective, standardized, and validated criteria [13]. Isolated symptomatic DVT was confirmed if there was a noncompression of a proximal or a distal deep vein on leg ultrasound. Symptomatic PE was confirmed if there was (i) a high clinical pretest probability and a high-probability ventilation-perfusion lung scan according to the Prospective Investigation of Pulmonary Embolism Diagnosis criteria; (ii) a proximal DVT diagnosed on ultrasonography in a patient with symptoms of PE; or (iii) a positive computed tomography pulmonary angiography showing a central filling defect outlined by contrast material or complete occlusion in a segmental or more proximal pulmonary artery.

The secondary outcomes were overall mortality and VTE by using the same objective criteria as the first VTE episode. All VTE recurrences were systematically adjudicated by experienced physicians not involved in patient care (F.C., C.L., and R.L.M.).

2.3 | Data collection

At baseline, the following variables and treatments were collected prospectively: age, gender, comorbidities (cardiovascular diseases, defined as ischemic stroke or myocardial infarction; pulmonary diseases; and cancer), personal and any family history of VTE, date of first symptoms and date of diagnosis of ALS, type (family or sporadic) and form (bulbar, spinal, peripheral, or associated with frontotemporal dementia) of ALS at the time of first symptoms and at the time of the diagnosis and member initially affected using the Medical Research Council score at the upper and lower portions of the arm, preventive or curative anticoagulation, and use of antiplatelet drugs and diuretics.

We also prospectively collected the following ALS-related variables during routine clinical visits every 3 to 6 months: motor skills (walking autonomy defined by walking independently or with human or material assistance, in a wheelchair, or bedridden, with walking perimeter expressed in meters), functional respiratory variables (forced expiratory volume in 1 second, forced vital capacity, and sniff test), clinical respiratory symptoms (presence of orthopnea and Sadoul dyspnea scale score), arterial blood gas (presence of hypoxemia [arterial pressure of oxygen Pa_{O_2} <80 mmHg] or hypercapnia [arterial pressure of carbon dioxide Pa_{CO_2} >45 mmHg]), and the use of noninvasive ventilation (NIV).

Regarding VTE, the following data were collected prospectively: (i) the date and (ii) the phenotype (ie, PE and/or DVT) of the acute episode, (iii) PE severity according to the simplified Pulmonary Embolism Severity Index, and (iv) circumstances classified as unprovoked or caused by a major transient risk factor (immobilization for >3 days, surgery <3 months earlier, fracture of the lower limb, pregnancy, and estrogen-containing pill), a minor transient factor (trauma of the lower limb without plaster cast and travel for >6 hours), a major persistent factor (cancer), or a minor persistent factor (chronic bowel diseases). Data on the type and duration of anticoagulant therapy and late complications, including chronic thromboembolic pulmonary hypertension, chronic thromboembolic venous disease, and VTE recurrence, were also prospectively collected.

2.4 | Statistical analysis

Quantitative variables were expressed as means (SD) or median (IQR), and qualitative variables were expressed as percentages with calculation of 95% CIs. Proportions were compared using chi-square test; continuous variables were compared using Student's *t*-test in case of normal distribution and Mann–Whitney U-test if the distribution was not normal. The annual incidence of VTE corresponds to the number of events per patient per year of risk exposure since the date of the diagnosis of ALS. Cumulative incidences of VTE were estimated using a competing risk analysis (ie, Fine–Gray method) with death as a competing risk. After selecting variables with a *P* value <.20, a multivariate analysis was performed using a Cox regression model. The hazard ratio (HR) and its 95% CIs were computed. A *P* value <.05 was considered statistically significant. SPSS software (version 20.0; SPSS, Inc) was used.

3 | RESULTS

From January 2009 to December 2019, 237 patients with ALS were eligible. Nine patients were excluded because of loss to follow-up, and 1 refused to participate. The remaining 227 patients were included in the analysis (Figure 1).

3.1 | Characteristics at baseline

Patients' characteristics at ALS diagnosis are presented in Table 1. Mean age was 64.8 years (SD, 11.9 years), and 112 patients (49.3%) were women. The mean body mass index was 25.2 kg/m^2 (SD, 5.1 kg/m^2). One hundred fifteen patients with ALS (58.1%) had a history of cardiovascular disease. The median time between first ALS symptoms and ALS diagnosis was 304.0 days (IQR, 153.0-486.0 days). Seven

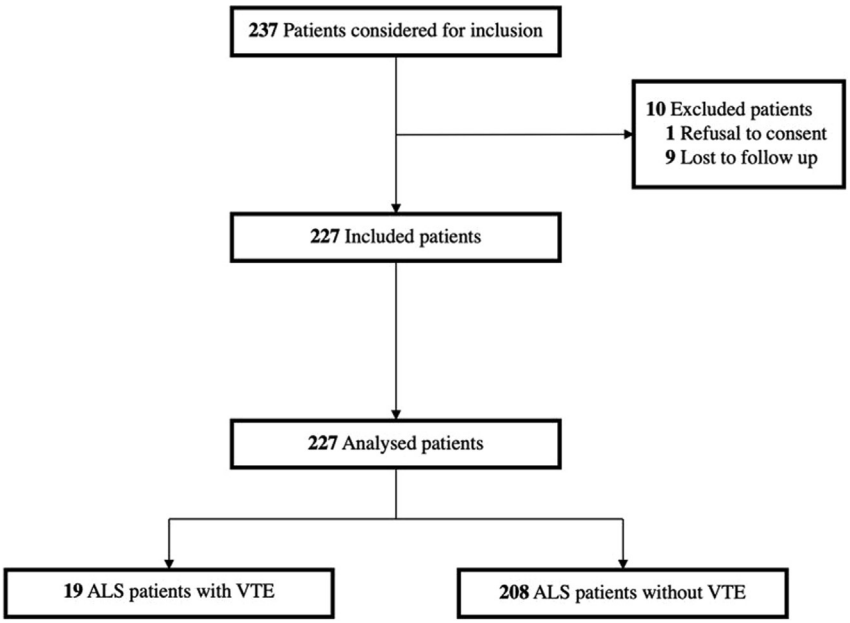

FIGURE 1 Flowchart of the Venous Thrombo-Embolism and Sclerosis Lateral Amyotrophic study. ALS, amyotrophic lateral sclerosis; VTE, venous thromboembolism.

TABLE 1 Baseline characteristics of study participants.

Variables	Patients with ALS (*N* = 227)	Patients with ALS and VTE (*n* = 19)	Patients with ALS without VTE (*n* = 208)	*P* value
Clinical				
Age (y), mean (SD)	64.8 (11.9)	65.5 (13.5)	64.7 (11.8)	.78
Female, *n/N* (%)	112/227 (49.3)	10/19 (52.6)	102/208 (49.0)	.76
BMI, mean (SD)	25.2 (5.1)	24.1 (3.6)	25.3 (5.2)	.44
Ethnicity *n/N* (%)	227/227 (100)	19/19 (100)	208/208 (100)	
Comorbidities, *n/N* (%)				
Cardiovascular	115/198 (58.1)	6/17 (35.3)	109/181 (60.2)	.08
Respiratory	23/198 (11.6)	1/17 (5.9)	22/181 (12.2)	.46
Cancer	33/198 (16.7)	2/17 (11.8)	31/181 (17.1)	.99
Personal history of VTE	7/227 (3.1)	2/19 (10.5)	5/208 (2.4)	.10
DVT	4/6 (66.7)	2/2 (100.0)	2/4 (50.0)	.47
PE	1/6 (16.7)	0/2 (0.0)	1/4 (25.0)	
Both	1/6 (16.7)	0/2 (0.0)	1/4 (25.0)	
Superficial thrombosis	1/1 (100.0)	-	1/1 (100)	-
Family history of VTE	3/227 (1.3)	2/19 (10.5)	1/208 (0.5)	.02
Ventilatory support, *n/N* (%)				
NIV	7/227 (3.1)	2/19 (10.5)	5/208 (2.4)	.11
Treatment				
Previous anticoagulation, *n/N*	27/227	0/19	27/208	.14
Preventive dose anticoagulation, *n*	10	0	10	
Curative dose anticoagulation, *n*	17	0	17	
Estrogen-containing pill, *n/N* (%)	5/227 (2.2)	0/19 (0.0)	5/208 (2.4)	.99
Antiplatelet, *n/N* (%)	40/227 (17.6)	1/19 (5.3)	39/208 (18.8)	.21
Diuretic, *n/N* (%)	10/227 (4.4)	3/19 (15.8)	7/208 (3.4)	.04
ALS clinical phenotype, *n/N* (%)				
Mixed	74/209 (35.4)	7/17 (41.2)	67/192 (34.9)	.77
Bulbar	31/209 (14.8)	2/17 (11.8)	29/192 (15.1)	
Spinal	88/209 (42.1)	8/17 (47.1)	80/192 (41.7)	
Peripheral	3/209 (1.4)	0/17 (0.0)	3/192 (1.6)	
Frontotemporal dementia	13/209 (6.2)	0/17 (0.0)	13/192 (6.8)	
Type, *n/N* (%)				
Sporadic	191/219 (87.2)	14/17 (82.4)	177/202 (87.6)	.46
Family	28/219 (12.8)	3/17 (17.6)	25/202 (12.4)	
Mobility characteristics				
MRC scale, mean (SD)				
Upper limb	27.0 (4.0)	26.0 (4.0)	27.0 (4.0)	.45
Lower limb	26.0 (5.0)	25.0 (6.0)	26.0 (5.0)	.30
Mobility				
Without assistance, *n/N* (%)	100/176 (56.8)	8/15 (53.3)	92/161 (57.1)	.76

(Continues)

TABLE 1 (Continued)

Variables	Patients with ALS (*N* = 227)	Patients with ALS and VTE (*n* = 19)	Patients with ALS without VTE (*n* = 208)	*P* value
With help, *n/N* (%)	67/176 (38.1)	7/15 (46.7)	60/161 (37.3)	
Wheelchair, *n/N* (%)	5/176 (2.8)	0/15 (0.0)	5/161 (3.1)	
Bedridden, *n/N* (%)	4/176 (2.3)	0/15 (0.0)	4/161 (2.5)	
Walking distance (m), median (IQR)[a]	200 (50-1500)	100 (70-2550)	250 (50-1500)	.04
Respiratory characteristics				
Sadoul score, median (IQR)	1.0 (0-3)	1.0 (1.0-3.0)	1.0 (0.0-3.0)	.43
Orthopnea, *n/N* (%)	33/157 (21.0)	4/14 (28.5)	30/143 (21.3)	.50
Functional respiratory test[b]				
FEV1, mean (SD)	2.32 (1.07)	2.43 (1.07)	2.31 (1.07)	.72
FEV1, mean %/theoretical value	90.0 (25.9)	94.5 (22.0)	90.4 (25.9)	.59
FVC, mean (SD)	2.85 (1.38)	3.13 (1.54)	2.82 (1.37)	.49
FVC, mean %/theoretical value	89.3 (27.4)	93.7 (26.2)	88.9 (27.6)	.59
Sniff test percentage, mean (SD)	53.5 (28.0)	52.1 (28.3)	53.6 (28.1)	.85
Blood gas, mean (SD)[c]				
$Paco_2$	44.24 (10.6)	37.11 (5.8)	43.66 (10.5)	.05
Pao_2	81.9 (22.4)	95.80 (35.0)	80.70 (20.8)	.05
HCO_3^-	27.20 (3.1)	24.30 (2.9)	27.50 (3.0)	.00
pH	7.38 (0.1)	7.38 (0.1)	7.38 (0.1)	.89
Delay in ALS diagnosis				
Time from first symptoms of ALS to ALS diagnosis, as a continuous variable (d), median (IQR)	304 (153-486)	123 (62-516)	334 (182-486)	.04
Time from first symptoms of ALS to ALS diagnosis, in tertiles (d), *n* (%)				
0-212 d	79 (34.8)	10 (52.6)	69 (33.2)	.02
213-406 d	72 (31.7)	4 (21.1)	68 (32.7)	.05
>406 d	76 (33.5)	5 (26.3)	71 (34.1)	.01
Survival				
Death, *n/N* (%)	175/227 (76.7)	14/19 (73.7)	161/208 (77.4)	.71
Time between first symptoms and death (d), median (IQR)	836 (497-1370)	837 (542-1416)	788 (425-1308)	.28

ALS, amyotrophic lateral sclerosis; BMI, body mass index; DVT, deep vein thrombosis; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HCO_3, bicarbonate; MRC, Medical Research Council; NIV, noninvasive ventilation; PE, pulmonary embolism; VTE, venous thromboembolism.
[a]Missing data in 175 patients.
[b]Missing data in 89 patients tested.
[c]Missing data in 127 patients.

patients with ALS already received NIV before the diagnosis of ALS: 1 for sleep apnea, 2 for diaphragm failure, 1 for alveolar hypoventilation, 2 for association sleep apnea and hypoventilation, and 1 after a respiratory failure.

3.2 | Annual incidence of VTE in patients with ALS

During a median follow-up period of 717 days (IQR, 488-1308 days), 19 patients developed an acute episode of symptomatic VTE, yielding

an annual incidence rate of 2.93% (95% CI, 1.88%-4.53%) (Figure 2). The cumulative incidence rate at 1, 2, and 4 years since the occurrence of first ALS symptoms was 3.1% (95% CI, 1.4%-6.0%), 7.4% (95% CI, 4.4%-11.5%) and 9.1% (95% CI, 5.7%-13.5%), respectively.

3.3 | Characteristics of VTE in patients with ALS

The characteristics of VTE in patients with ALS are summarized in Table 2. The median time between first ALS symptoms and the occurrence of VTE was 549 days (IQR, 273-699 days). Among the 19 VTE events, 4 were symptomatic isolated PE (21.1%), 3 were symptomatic PE associated with DVT (15.8%), and 12 were isolated DVT (63.2%). Ten VTEs were unprovoked (62.5%), 5 were provoked by a major transient factor (31.3%) (mainly due to a surgical cause and immobilization), and 1 (6.3%) was related to a minor transient factor (travel for >6 hours). Two patients with VTE had a family history of thrombosis.

3.4 | VTE recurrence in patients with ALS

Recurrent VTE occurred in 5 of 19 patients (26.3%) after anticoagulation discontinuation (Table 2). Among these 5 patients, the first episode of VTE after inclusion occurred as DVT in all patients, and recurrent VTE presented as an isolated PE in 2, PE and DVT in 1, and an isolated DVT in 2 patients. The duration of anticoagulation and the delay of recurrence delays are reported in Table 3. The duration of anticoagulation after VTE ranged between 1.5 and 6 months. VTE recurrence occurred within 4 months after stopping anticoagulant treatment in 4 patients. No recurrent VTE occurred under anticoagulation.

3.5 | Survival

The survival of patients with ALS is detailed in Table 1. The median survival of the overall ALS population was 836 days (IQR, 497-1370 days). VTE did not significantly influence survival of the ALS population: the median survival of patients with ALS in the VTE group and the no-VTE group was 837 days (IQR, 542-1416 days) and 788 days (IQR, 425-1308 days), respectively (P = .28).

3.6 | Predictive factors of VTE in patients with ALS

In multivariable analysis (Table 4), the presence of family history of thrombosis (HR, 15.24; 95% CI, 1.72-134.84; P = .01), the use of NIV at ALS diagnosis (HR, 6.98; 95% CI, 1.09-44.59; P = .04), the time between first ALS symptoms and ALS diagnosis (HR, 5.48; 95% CI, 1.57-19.11, when the time period was <213 days, and HR, 1.40; 95% CI, 0.31-6.37, when the time period was ≥213 and <406 days, as compared to the reference group [time, >406 days; P = .01]), and the presence of diuretics (HR, 5.79; 95% CI, 1.28-26.16; P = .02) were associated with an increased risk of VTE during follow-up.

4 | DISCUSSION

In this prospective cohort of patients with ALS followed in the ALS center in Brest University Hospital, we found an annual incidence rate of 2.93% (95% CI, 1.88%-4.53%) and a VTE recurrence rate of 26.3% at 3 months after anticoagulation discontinuation. Risk factors associated with a first episode of VTE were the presence of a family history of VTE, the use of NIV at ALS diagnosis, a shorter time period between first ALS symptoms and ALS diagnosis, and diuretic

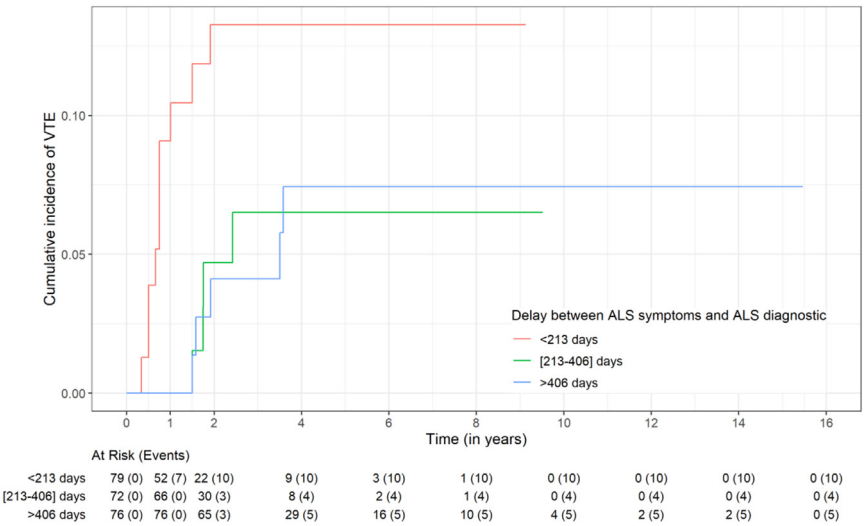

FIGURE 2 Cumulative incidence of venous thromboembolism (VTE) in the amyotrophic lateral sclerosis (ALS) population during follow-up.

TABLE 2 Venous thromboembolism characteristics.

Clinical presentation of VTE		*n/N* (%)
Symptomatic isolated PE		4/19 (21.1)
Symptomatic PE associated with DVT		3/19 (15.8)
Symptomatic isolated DVT		12/19 (63.2)
Thrombus location and severity, *n/N* (%)		
PE		
Proximal (lobar or more proximal)		2/6 (16.7)
Segmental		3/6 (50.0)
Subsegmental		1/6 (16.7)
Severity of PE[a]		
Low risk		1/5 (20.0)
Intermediate-to-low risk		3/5 (60.0)
Intermediate-to-high risk		1/5 (20.0)
High risk		0 (0.0)
DVT		
Proximal		11/14 (78.6)
Distal		3/14 (21.4)
Unilateral		12/14 (85.7)
Bilateral		2/14 (14.3)
Ipsilateral to the deficit limb		7/11 (63.6)
Other thromboses		
Superficial thrombosis		1/19 (5.3)
Muscular thrombosis		2/19 (10.5)
Risk factors, *n/N* (%)		
Unprovoked		10/16 (62.5)
Major transient risk factor		5/16 (31.3)
Surgery in the past 3 mo		2/16 (12.5)
Immobilization for ≥3 d in the past 3 mo		3/16 (18.8)
Fracture in the past 3 mo		0/16 (0.0)
Pregnancy in the past 3 mo		0/16 (0.0)
Estrogen-containing pill		0/16 (0.0)
Minor transient risk factor		1/16 (6.3)
Minor trauma		0/16 (0.0)
6-h travel		1/16 (6.3)
Major persistent risk factor		0/15 (0.0)
Cancer		0/15 (0.0)
Minor persistent risk factor		0/15 (0.0)
Inflammatory bowel diseases		0/15 (0.0)
Treatment, *n/N* (%)		
Treatment	Acute phase[b]	After acute phase
UFH	1/14 (7.1)	0/14 (0.0)
LMWH	6/14 (42.9)	0/14 (0.0)
DOAC	5/14 (35.7)	11/14 (78.6)
Fondaparinux	2/14 (14.3)	0/14 (0.0)
VKA	2/14 (14.3)	3/14 (21.4)
VTE complications, *n/N* (%)		
Recurrent VTE[c]		5/19 (26.3)
Symptomatic isolated PE		2/5 (40.0)
Symptomatic PE associated with DVT		1/5 (20.0)
Symptomatic isolated DVT		2/5 (40.0)
Chronic sequelae		1/19 (5.3)
CTEPH		0/19 (0.0)
CTED		1/19 (5.3)
Death		0/19 (0.0)

CTED, chronic thromboembolic disease; CTEPH, chronic thromboembolic pulmonary hypertension; DOAC, direct oral anticoagulant; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; PE, pulmonary embolism; UFH, unfractionated heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.

[a]Assessed with simplified Pulmonary Embolism Severity Index, the presence of right ventricular dysfunction, and troponin level.

[b]The acute phase treatment represents the treatment at venous thromboembolism diagnosis.

[c]No recurrent venous thromboembolism occurred under anticoagulation.

use. Mortality in patients with VTE was not higher than those without VTE.

The annual incidence rate of VTE observed in this study is consistent with other studies [6–8]. In a post hoc analysis of a subgroup of 501 patients with ALS selected from 3 randomized, double-blind trials evaluating various specific treatments of this neurodegenerative disease and after excluding patients receiving topiramate treatment, Qureshi et al. [7] found an annual incidence rate of 2.7% of DVT. In another large retrospective study including 438 patients with ALS followed for 4 years, Elman et al. [6] reported an annual incident rate of 2.97%. In a prospective study of 50 patients with ALS who underwent systematic lower limb ultrasound at baseline and at 6 and 12 months, Gladman et al. [8] found a cumulative incidence rate of symptomatic VTE of 5% at 1 year of follow-up. This rate reached 11% when asymptomatic cases were taken into account. Of note, the TESLA study is the first prospective study in patients with ALS where VTE diagnosis was confirmed based on predefined and validated criteria in accordance with international guidelines, and all VTE events were adjudicated blindly. Thus, the observed annual incidence rate of a first VTE in patients with ALS is likely to be valid and appears to be higher than that observed in the general population (1-2 VTE events per person per year) [1].

In this study, an association between family history of VTE and an increased risk of VTE was observed in patients with ALS. This result is

TABLE 3 Venous thromboembolism recurrence analysis.

Patient no.	Personal history of VTE	Time between first ALS symptoms and first VTE event during follow-up (d)	VTE after diagnosis of ALS	Type of VTE	Anticoagulation treatment duration (mo)	Date of recurrent VTE	Delay between treatment discontinuation and VTE recurrence (mo)	Type of VTE
1	Yes	242.00	July 2019	Isolated proximal DVT	3	December 2019	3	PE and DVT
2	No	549.00	February 2019	Isolated proximal DVT	3	August 2019	4	Isolated DVT
3	No	701.00	June 2016	Isolated distal DVT	1.5	December 2017	15.5	Isolated PE
4	No	699.00	July 2014	Isolated proximal DVT	6	March 2015	3	Isolated PE
5	No	366.00	August 2008	Isolated proximal DVT	6	March 2009	2	Isolated DVT

ALS, amyotrophic lateral sclerosis; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism.

consistent with previous studies in the general population, which found a relationship between family history of VTE and risk of VTE [14]. Such an association between family history of VTE and risk of VTE has also been found in populations with a high risk of thrombosis, such as cancer [15] or chronic bowel inflammatory disease [16]. Of note, because thrombophilia was not systematically searched, we could not determine whether the presence of inherited thrombophilia would be an additional independent risk factor of VTE in patients with ALS. Surprisingly, only a trend toward an increased risk of VTE was observed in patients with a previous personal history of VTE (ie, VTE occurring before ALS symptoms). This is likely due to the lack of power; in addition, we found that a personal history of VTE was also strongly correlated with a family history of thrombosis, which later appeared as a much stronger predictor for VTE in univariable analysis in this specific population with neurodegenerative disease.

Interestingly, we found an association between a shorter time period between first ALS symptoms and ALS diagnosis and the risk of VTE: patients having a diagnosis of ALS less than 213 days after first

TABLE 4 Risk factors of venous thromboembolism in the amyotrophic lateral sclerosis population.

	Univariable analysis		Multivariable analysis	
Variables	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
CV comorbidity	0.51 (0.19-1.34)	.169	-	-
Personal history of thrombosis[a]	5.85 (1.32-26.0)	.02	-	-
Family history of thrombosis	13.53 (3.06-59.82)	.001	15.24 (1.72-134.84)	.01
Diagnosis delay as a continuous variable	0.98 (0.996-1.000)	.03	-	-
Diagnostic time in tertiles[b]				
>406 d	Ref	.023	Ref	.01
213-406 d	1.25 (0.33-4.71)	.74	1.40 (0.31-6.37)	.66
<213 d	3.92 (1.31-11.70)	.014	5.48 (1.57-19.11)	.01
Antiplatelet	0.26 (0.04-1.94)	.189	-	-
Diuretic	4.35 (1.27-14.95)	.02	5.79 (1.28-26.16)	.02
NIV	4.66 (1.06-20.57)	.042	6.98 (1.09-44.59)	.04

CV, cardiovascular; NIV, noninvasive ventilation; Ref, reference.

[a]Kappa coefficient was 0.39, $P < .001$ for personal history of venous thromboembolism (VTE); personal history of VTE was not included in the multivariable model as it was less significant than a personal history of VTE in the univariable model.

[b]Diagnostic delay as expressed in tertiles (not as a continuous variable) was included in the multivariable model.

ALS symptoms had a 5-fold increased risk of VTE compared to those being diagnosed with ALS more than 406 days after first ALS symptoms. One plausible hypothesis is that highly symptomatic and rapidly progressive ALS profiles might have more aggressive and active inflammatory components and, subsequently, a higher thrombosis risk. Such a hypothesis is also reinforced by the higher risk of VTE observed in association with NIV, which represents patients with a more severe status of the ALS disease. The main justification of NIV in our ALS population was alveolar hypoventilation and diaphragmatic failure as assessed by the sniff test and by the severity of this neurodegenerative disease. Whether NIV increases the risk of VTE because of reduced mobility or a more severe form of ALS remains undetermined. Of note, such a hypothesis is not supported by others: in a study on 50 patients, there was a trend toward an association between VTE and longer disease durations since first symptoms (P = .054) [8]. Thus, the pathophysiological explanation of the association between VTE and ALS is not yet understood, and it appears to be explained not only by immobilization indices but also by the natural course of ALS.

Surprisingly, there was a significant association between diuretic treatment and the occurrence of VTE (P = .023): the majority of patients were treated with thiazide diuretics, 2 with loop diuretics, and 2 with potassium-sparing diuretics. In the literature, no data were found about this association. These treatments were mainly administered for cardiovascular comorbidities, especially arterial hypertension. The dehydration and hypovolemia induced by these treatments might be responsible for renal failure and a procoagulant state. In a prospective observational study including 102 patients who experienced an acute ischemic stroke, Kelly et al. [17] found a relationship between dehydration and the development of VTE (odds ratio, 2.8-4.7).

Lastly, we observed a very high rate of VTE recurrence (26.3%), which occurred shortly after stopping anticoagulant therapy (median time of 3 months), raising the question of the optimal duration of anticoagulant treatment after a first VTE in patients with ALS. In a multicenter prospective cohort study published in 2021 [9] including 1881 patients with a first symptomatic VTE who were followed for a median period of 4.8 years after anticoagulation discontinuation, ALS was found to be associated with a very high risk of recurrent VTE (HR, 5.74; 95% CI, 1.79-18.37; $P < .001$). These observations suggest that anticoagulation should not be stopped when these patients develop VTE.

Based on the results of our study, the introduction of preventive anticoagulant treatment at the diagnosis of ALS might be considered in patients with a family history of thrombosis, who are already using NIV, and whose ALS diagnosis was made early after the onset of symptoms. However, additional studies are needed in order to confirm these findings and to identify more precisely high thrombotic risk profiles in the ALS population. Indeed, using preventive anticoagulation may have an impact on quality of life by using subcutaneous injection of heparin and may expose these fragile patients to a higher bleeding risk. Thus, VTE prevention management needs further investigations with a large prospective and randomized study.

Several limitations should be underlined. First, patients with ALS were included in a single university hospital center, which is a reference center of VTE. This expertise in VTE might have led to suspecting and diagnosing VTE more often than in standard care centers. Second, the sample size was moderate, which lowered the ability to identify predictors for VTE. Third, some data regarding respiratory functional test, blood gas, and amyotrophic lateral sclerosis Functional Rating scale-revised score were missing, and these parameters regarding the risk of VTE could not be analyzed. However, this study presents several strengths. First, the TESLA study is one of the rare prospective studies of patients with ALS using predefined and validated criteria of VTE; all VTE events were adjudicated blindly. Second, this is the first study using a validated definition of ALS based on El Escorial criteria with a standard predefined prospective follow-up. Third, in contrast with other studies, ventilatory and motor parameters were carefully detailed. Finally, we were able to identify several predictive factors for VTE in patients with ALS and observed a high risk of recurrence early after stopping anticoagulation.

5 | CONCLUSION

The annual incidence of a first episode of symptomatic acute VTE in the ALS population is high. Family history of VTE, use of NIV at ALS diagnosis, use of diuretics, and shorter time between first ALS symptoms and ALS diagnosis were associated with an increased risk of a first episode of VTE in these patients. However, the prothrombotic risk profile of ALS remains to be assessed in a larger prospective study in order to optimize preventive VTE management in this specific and fragile population.

FUNDING

Authors do not declare any funding for this study.

ETHICS STATEMENT

The protocol has been approved by the local ethical committee (29BRC19.0236) and recorded in ClinicalTrials.gov (NCT04446325). All patients with venous thromboembolism provided written informed consent.

AUTHOR CONTRIBUTIONS

C.T. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: A.B., C.T., S.G., C.G.-G. Acquisition of data: A.B., S.G.. Statistical analysis: F.C.. Analysis and interpretation of data: all. Drafting of the manuscript: A.B., S.G., F.C., C.T. Critical revision of the manuscript for important intellectual content: all. Final approval of the manuscript: all. Administrative, technical, or material support: S.G., F.C., C.T. Study supervision: F.C., C.T.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

TWITTER

Francis Couturaud @fcouturaud

REFERENCES

[1] Oger E. Incidence of venous thromboembolism: a community-based study in Western France. EPI-GETBP Study Group. Groupe d'Etude de la Thrombose de Bretagne Occidentale. *Thromb Haemost*. 2000;83:657–60.

[2] Marin B, Boumédiene F, Logroscino G, Couratier P, Babron MC, Leutenegger AL, et al. Variation in worldwide incidence of amyotrophic lateral sclerosis: a meta-analysis. *Int J Epidemiol*. 2017;46:57–74.

[3] Inserm. Sclérose latérale amyotrophique (SLA) / maladie de Charcot. https://www.inserm.fr/information-en-sante/dossiers information/sclerose-laterale-amyotrophique-sla-maladie-charcot; 2020 [accessed July 27, 2020].

[4] Torny F, Lacoste M, Nguyen JM, Tymoczko-Nguyen ME, Couratier P. Étude des causes du retard au diagnostic de la sclérose latérale amyotrophique. *Rev Neurol (Paris)*. 2006;162:617–22.

[5] Brooks BR. Diagnostic dilemmas in amyotrophic lateral sclerosis. *J Neurol Sci*. 1999;165:S1–9.

[6] Elman LB, Siderowf A, Houseman G, Kelley M, McCluskey LF. Venous thrombosis in an ALS population over four years. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2005;6:246–9.

[7] Qureshi MM, Cudkowicz ME, Zhang H, Raynor E. Increased incidence of deep venous thrombosis in ALS. *Neurology*. 2007;68:76–7.

[8] Gladman M, Dehaan M, Pinto H, Geerts W, Zinman L. Venous thromboembolism in amyotrophic lateral sclerosis: a prospective study. *Neurology*. 2014;82:1674–7.

[9] Le Mao R, Orione C, de Moreuil C, Tromeur C, Hoffmann C, Fauché A, et al. Risk stratification for predicting recurrent venous thromboembolism after discontinuation of anticoagulation: a post hoc analysis of a French prospective multicentre study. *Eur Respir J*. 2022;60:2103002. https://doi.org/10.1183/13993003.03002-2021

[10] Gil J, Funalot B, Verschueren A, Danel-Brunaud V, Camu W, Vandenberghe N, et al. Causes of death amongst French patients with amyotrophic lateral sclerosis: a prospective study. *Eur J Neurol*. 2008;15:1245–51.

[11] Corcia P, Pradat PF, Salachas F, Bruneteau G, le Forestier N, Seilhean D, et al. Causes of death in a post-mortem series of ALS patients. *Amyotroph Lateral Scler*. 2008;9:59–62.

[12] Brooks BR, Miller RG, Swash M, Munsat TL. World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. *Amyotroph Lateral Scler Other Motor Neuron Disord*. 2000;1:293–9.

[13] Konstantinides SV, Meyer G, Becattini C, Bueno H, Geersing GJ, Harjola VP, et al. 2019 ESC Guidelines for the diagnosis and management of acute pulmonary embolism developed in collaboration with the European Respiratory Society (ERS). *Eur Heart J*. 2020;41:543–603.

[14] Couturaud F, Leroyer C, Tromeur C, Julian JA, Kahn SR, Ginsberg JS, et al. Factors that predict thrombosis in relatives of patients with venous thromboembolism. *Blood*. 2014;124:2124–30.

[15] Heraudeau A, Delluc A, Le Henaff M, Lacut K, Leroyer C, Desrues B, et al. Risk of venous thromboembolism in association with factor V leiden in cancer patients—the EDITH case-control study. *PLoS One*. 2018;13:e0194973. https://doi.org/10.1371/journal.pone.0194973

[16] Keller K, Sivanathan V, Schmitt VH, Ostad MA, Münzel T, Espinola-Klein C, et al. Incidence and impact of venous thromboembolism in hospitalized patients with Crohn's disease. *Thromb Res*. 2022;219:77–85.

[17] Kelly J, Hunt BJ, Lewis RR, Swaminathan R, Moody A, Seed PT, et al. Dehydration and venous thromboembolism after acute stroke. *QJM*. 2004;97:293–6.