Incidence and risk factors of venous thromboembolism in patients with amyotrophic lateral sclerosis: A systematic review and meta-analysis

Incidences et facteurs de risque de la thromboembolie veineuse chez les patients atteints de sclérose latérale amyotrophique : Une revue systématique et une méta-analyse

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Abstract

Aims: This systematic review and meta-analysis aimed to determine the annual incidence rate of venous thromboembolism (VTE) and identify risk factors of VTE in amyotrophic lateral sclerosis (ALS) patients.

Methods: A comprehensive search of three databases was conducted up to April 8, 2024, to identify longitudinal studies reporting VTE incidence in ALS patients. The included studies were either prospective or retrospective, following up with ALS patients. Quality assessment was performed using the NIH tool for observational cohort studies. Meta-analysis was conducted using Open Meta Analyst, employing a random-effect model. Subgroup, Meta-regression, and sensitivity analyses were also carried out.

Results: Our analysis included eight studies comprising a total of 26,758 ALS patients that met the inclusion criteria. The pooled annual incidence of VTE across all studies was found to be 22 cases per 1,000 person-year (95% CI = 18 to 27). Subgroup analysis revealed that the annual incidence of VTE in males was 19 cases per 1,000 person-year (95% CI = 15 to 22), while in females, it was 20 cases per 1,000 person-year (95% CI = 16 to 25). Leave-one-out analysis demonstrated that the incidence ranged from 21 to 28 cases per 1,000 person-year when excluding each study individually. Meta-regression analysis did not find a significant association between age and the risk of VTE (P = 0.079). Based on the included studies, risk factors of VTE in ALS patients included a history of VTE, non-invasive ventilation, immobility, and decreased functional status.

Conclusion: Patients with ALS face a higher risk of developing VTE compared to individuals of the same age. These findings underscore the importance of implementing preventive measures and closely monitoring VTE in ALS patients.

Key words: Amyotrophic Lateral Sclerosis, Motor Neurone Disease, Neurodegenerative diseases, Pulmonary embolism, Venous thromboembolism

Résumé

Objectifs: Cette revue systématique et cette méta-analyse avaient pour objectif de déterminer le taux d'incidence annuel de la maladie thromboembolique veineuse (MTEV) et d'identifier les facteurs de risque de la MTEV chez les patients atteints de sclérose latérale amyotrophique (SLA).

Méthodes: Une recherche exhaustive a été menée dans trois bases de données jusqu'au 8 avril 2024 afin d'identifier des études longitudinales rapportant l'incidence de la TEV chez les patients atteints de SLA. Les études incluses étaient soit prospectives, soit rétrospectives, et suivaient les patients atteints de SLA. Une évaluation de la qualité a été réalisée à l'aide de l'outil du NIH pour les études de cohorte observationnelles. La méta-analyse a été réalisée à l'aide d'Open Meta Analyst, en utilisant un modèle à effets aléatoires. Des analyses de sous-groupes, de méta-régression et de sensibilité ont également été effectuées.

Résultats: Notre analyse comprenait huit études portant sur un total de 26 758 patients atteints de SLA répondant aux critères d'inclusion. L'incidence annuelle regroupée de la MTEV dans l'ensemble des études était de 22 cas pour 1 000 personnes-année (IC à 95% = 18 à 27). L'analyse de sous-groupes a trouvé une incidence annuelle de MTEV de 19 cas pour 1 000 personnes-année (IC à 95% = 15 à 22) chez les hommes, et de 20 cas pour 1 000 personnes-année (IC à 95% = 16 à 25) chez les femmes. L'analyse de retrait individuel a montré que l'incidence variait de 21 à 28 cas pour 1 000 personnes-année en excluant chaque étude individuellement. L'analyse de méta-régression n'a pas trouvé d'association significative entre l'âge et le risque de MTEV (P = 0,079). Selon les études incluses, les facteurs de risque de la MTEV chez les patients atteints de SLA comprenaient les antécédents de MTEV, la ventilation non-invasive, l'immobilité et la diminution de l'état fonctionnel.

Conclusion: Les patients atteints de SLA présentent un risque plus élevé de développer une TEV par rapport aux personnes du même âge. Ces résultats soulignent l'importance de mettre en œuvre des mesures préventives et de surveiller étroitement la MTEV chez les patients atteints de SLA.

Mots clés: Sclérose latérale amyotrophique, Maladie des motoneurones, Maladies neurodégénératives, Embolie pulmonaire, Thromboembolie veineuse.

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Introduction

Amyotrophic lateral sclerosis (ALS), commonly known as Lou Gehrig's disease, is a rare neurodegenerative disorder characterized by progressive loss of motor neurons, resulting in muscle weakness and atrophy, ultimately leading to complete loss of mobility [1]. Despite its rarity, ALS is the most prevalent motor neuron disease, with an average survival time of approximately 30 months from symptom onset [2]. ALS manifests with wasting and gradual weakening of muscles, leading to progressive loss of motor function and eventual respiratory muscle failure [1,3].

Muscular dysfunction, especially respiratory muscle failure, is the leading cause of death in ALS patients. However, venous thromboembolism (VTE) has also been identified as a significant contributing factor to sudden death [4]. Reduced lower limb mobility in ALS patients is hypothesized to increase the risk of VTE, particularly deep vein thrombosis [5]. Two prospective studies have shown incidence rates of venous thromboembolism in ALS patients ranging from 29 to 85 cases per 1000 patients per year [6,7]. Another study reported a rate exceeding 110 cases per 1000 patients [5]. These reported rates are significantly higher than those in the general population of the same age group [8]. In one study investigating causes of death among ALS patients, pulmonary embolism accounted for 6% of the cases [9]. Given the limited literature and variability in reported incidence rates of venous thromboembolism in ALS, this systematic review and meta-analysis aims to establish the overall incidence rate of venous thromboembolism and explore potential risk factors associated with this complication in ALS patients.

Methods

Search Strategy and Selection Criteria

This study was conducted following the guidelines for systematic reviews and meta-analyses (PRISMA) [10]. A comprehensive search was performed in three databases (PubMed, Scopus, and Web of Science) on April 8, 2024, using appropriate search terms as detailed in Table 1. No filters were applied to the article type or language during the search process. Following the search, all citations were uploaded to a reference management software (Rayyan) for screening and selection [11]. Screening and selection were performed without removing duplicates to ensure no relevant articles were missed. Two researchers independently screened and filtered the studies in two stages: initial screening of titles and abstracts based on inclusion criteria, followed by full-text review of selected articles. References and citations of the included studies were also checked to ensure comprehensive coverage.

Table 1. illustrates the search terms used

(«Motor Neuron Disease» OR «Motor System Disease» OR «Gehrig Disease» OR «Lou Gehrig's Disease» OR «Lou Gehrig» OR «Charcot Disease» OR «Amyotrophic Lateral Sclerosis» OR «Lateral Sclerosis» OR «Guam Disease» OR ALS)
("Pulmonary Embolism" OR "Venous Thrombosis" OR "Venous Thromboembolism")

Inclusion and Exclusion Criteria

This study aimed to summarize published literature on the incidence rates of VTE in ALS patients and explore associated risk factors, demographic characteristics, and clinical features related to venous thromboembolism occurrence. Inclusion criteria encompassed longitudinal studies (either prospective or retrospective) with follow-up and monitoring of VTE occurrence in ALS patients over a specified period. Exclusion criteria included cross-sectional studies, as they lack the follow-up and monitoring required to measure incidence rates. Experimental studies, reviews, correspondences, and conference abstracts were also excluded.

Data Extraction and Quality Assessment

Data extraction was independently performed by two researchers using an online data extraction form, followed by review by a third researcher. Extracted data included: (1) first author's name, publication year, and country, (2) study outcomes, (3) sample size, and (4) methodological study quality aspects. The quality of included studies was assessed using the NIH tool for observational cohort studies, adapted to better fit the design of included studies [12].

Statistical Analysis

All statistical analyses were conducted using Open Meta Analyst software and random-effects meta-analysis models [13,14]. The incidence rate of VTE refers to the number of new cases recorded during a specified time period. Incidence rates were standardized across studies as annual rates per 1000 patients, and overall incidence rates were calculated using pooled incidence rates with a 95% confidence interval (CI). Subgroup meta-analyses were conducted by gender, and sensitivity analysis was performed by excluding one study at a time. The heterogeneity among the included studies was assessed using the chi-square P value and the I2 test. High heterogeneity was indicated by a chi-square P value of less than 0.1 and I2 values of ≥ 50%.

Results

Characteristics of Included Studies

A total of 620 studies were identified from the database search. Following title and abstract screening, 20 studies proceeded to full-text assessment. Eight studies met the inclusion criteria and were included in the review

and meta-analysis [5–7,15–19], while 12 studies were excluded for not meeting the criteria (Figure 1).

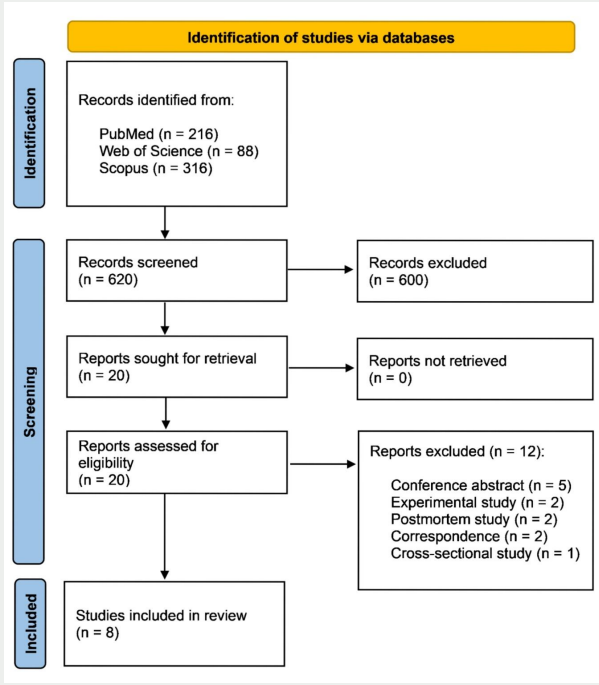

Figure 1. PRISMA flow diagram

Three studies were conducted in the United States and one in Canada, with the remaining studies from Europe and Australia (Table 2). The included studies varied widely in sample sizes, ranging from 44 to 21,163 participants. Overall, the quality of included studies was moderate, as shown in Table 3.

Table 2. demonstrates the characteristics of the included studies

Study	Design	Country	Sample size	Males %	VTE incidence per 1000 person-year
Barnabe 2023	Prospective	France	277	51.7	29
Caballero 2022	Prospective	Spain	44	44.5	85
Elman 2005	Retrospective	US	438	55.0	33
FORREST 2014	Retrospective	Australia	130	-	38
Gladman 2014	Prospective	Canada	50	72.0	111
Goldacre 2024	Retrospective	UK	21163	54.8	19
Kupelian 2023	Retrospective	US	4205	56.9	20
Qureshi 2007	Retrospective	US	501	-	27

Table 3. demonstrates the quality assessment of the included studies using the NIH tool

Item	Barnabe 2023	Caballero 2022	Elman 2005	FORREST 2014	Gladman 2014	Goldacre 2024	Kupelian 2023	Qureshi 2007
Was the research question or objective in this paper clearly stated?	Y	Y	Y	Y	Y	Y	Y	Y
Was the study population clearly specified and defined?	Y	Y	Y	Y	Y	Y	Y	Y
Was the participation rate of eligible persons at least 50%?	Y	N	NR	NR	NR	NA	NA	NA
Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Y	Y	NR	NR	Y	NR	Y	Y
Was the sample size calculation and its effect on the study power clearly stated?	N	Y	N	N	N	NA	NA	NA
Were participants confirmed to have ALS?	Y	Y	NR	Y	Y	NR	Y	NR
Was the follow-up period sufficient to determine the causal relationship between ALS and VTE?	Y	Y	Y	Y	Y	Y	CD	CD
Did the study reported the type and duration of ALS and its effect on the occurrence of VTE?	Y	CD	Y	Y	Y	Y	Y	CD
Were the exposure measures clearly defined, valid, reliable, and implemented consistently across all study participants?	Y	Y	Y	CD	Y	CD	Y	CD
Was loss to follow-up after baseline 20% or less?	Y	NR	NR	NR	NR	NR	NR	NR
Were potential confounding variables measured and adjusted statistically for their impact on the results?	Y	Y	CD	NR	Y	Y	Y	NR

Y: yes; **N**: no; **CD**: cannot determine; **NA**: not applicable; **NR**: not reported

Incidence Rates of Venous Thromboembolism

Incidence rates of VTE varied among studies, ranging from 19 to 111 cases per 1000 persons annually. The meta-analysis indicated an overall incidence rate across all studies of 22 cases per 1000 person-year (95% CI = 18 to 27) (Figure 2). Due to variability in incidence rates and sample sizes among studies, sensitivity analysis was conducted. Sensitivity analysis showed incidence rates of VTE ranging from 21 to 28 cases per 1000 person-year in the studied population (Figure 3). Subgroup meta-analysis by gender showed an incidence rate among males of 19 cases per 1000 person-year (95% CI = 15 to 22) (Figure 4). Among females, the incidence rate was 20 cases per 1000 person-year, with a 95% CI ranging from 16 to 25 (Figure 4).

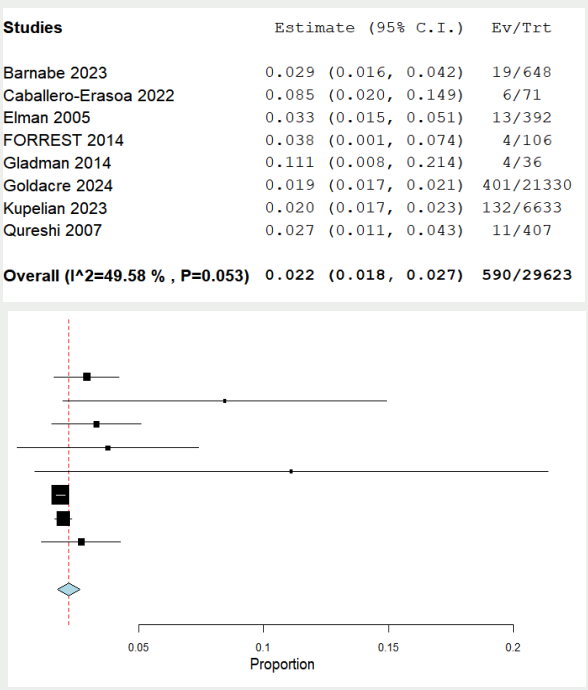

Figure 2. Forest plot illustrating the incidence rate of VTE across the included studies

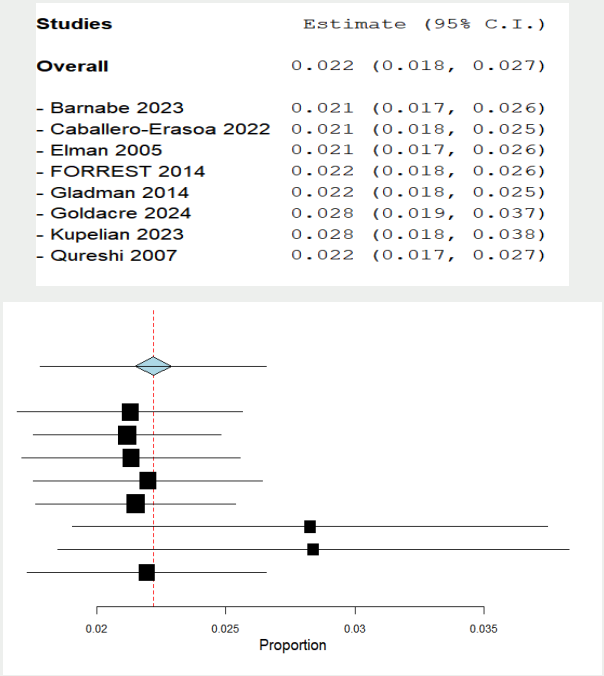

Figure 3. Forest plot demonstrating the sensitivity analysis of VTE incidence, evaluating the impact of excluding individual studies on the overall results.

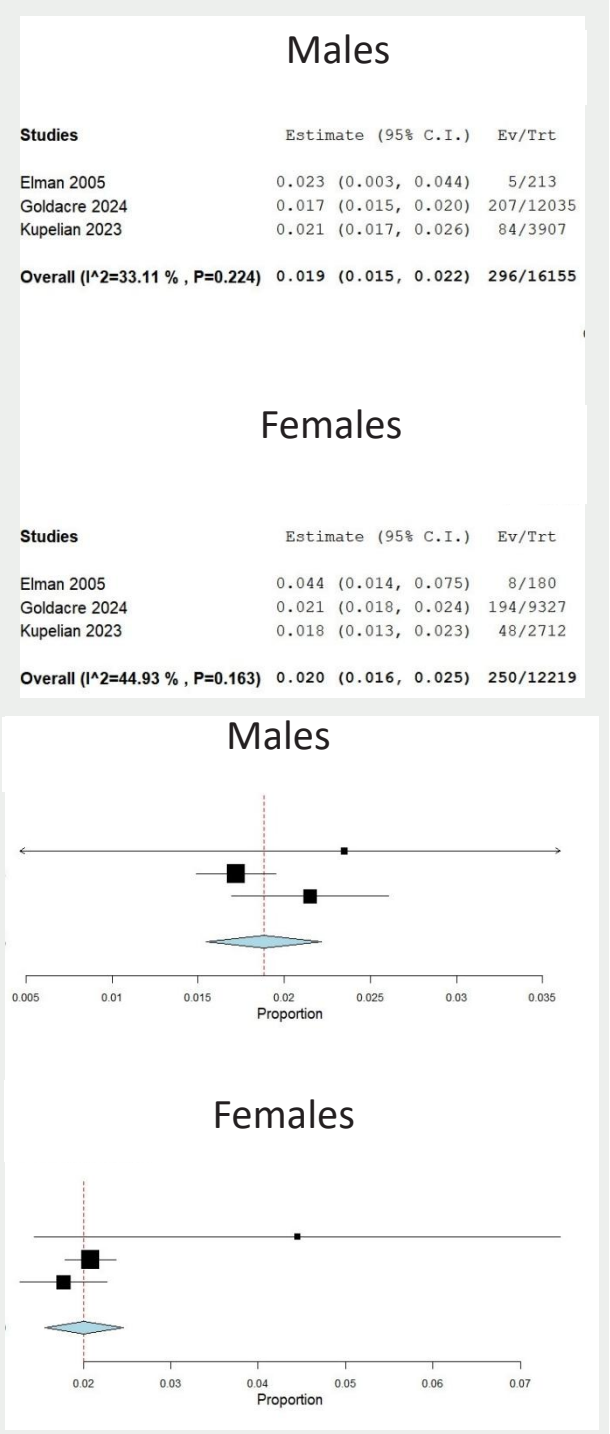

Figure 4. Subgroup analysis by gender, presenting the incidence rate of VTE in male and female

Risk Factors

Meta regression analysis did not show a significant relationship between the incidence rate of VTE and patient age at study initiation (P value = 0.079) (Figure 5). However, Goldacre and Kupelian studies reported a higher risk ratio for VTE occurrence in younger ALS patients compared to age-matched controls [17,18]. Barnabe's study indicated risk factors for VTE occurrence among patients included non-invasive ventilation, short duration between symptom onset and ALS diagnosis, and a history of VTE [6]. All cases of VTE in Caballero's study were associated with severe immobility and wheelchair dependence [7]. Immobility was also identified as a risk factor for VTE occurrence in Elman and Gladman studies [5,15]. Furthermore, all studies reported that functional status decline and deterioration were significant risk factors for VTE occurrence.

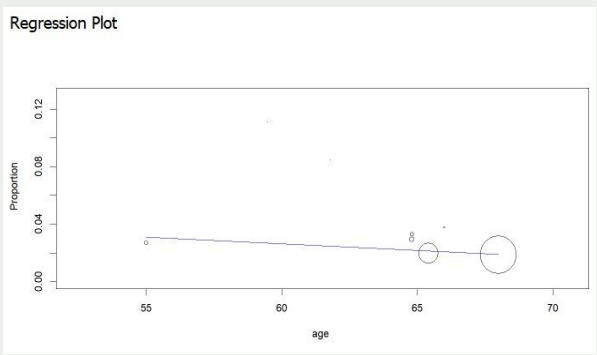

Figure 5. Meta-regression analysis investigating the association between VTE incidence and the age of patients at baseline in the included studies.

Discussion

VTE, which includes deep vein thrombosis and pulmonary embolism, is a serious medical condition characterized by high rates of morbidity and mortality. Neurodegenerative diseases affecting the lower limbs, such as ALS, represent a significant risk factor for VTE. Risk factors are further increased in ALS patients, including immobility, advancing age, and respiratory muscle weakness. Therefore, we conducted this study to estimate the incidence rate of VTE in ALS patients and summarize associated risk factors.

Incidence rates in the included studies ranged from 19 to 111 cases per 1000 persons annually, while the meta-analysis showed an overall incidence rate of 22 cases per 1000 persons annually with a 95% CI ranging from 18 to 27. This variability among studies may be attributed to differences in sample sizes, as incidence rates converge significantly in studies with larger sample sizes [17,18]. Subgroup meta-analysis by gender indicated an incidence rate of 19 cases per 1000 persons annually among males and 20 cases per 1000 persons annually among females. This slight increase in females is consistent with some epidemiological studies, which may be attributed to factors such as obesity, use of exogenous hormones, and visceral fat [20]. Our study also identified several accompanying risk factors for patients that may increase the likelihood of developing VTE. Our study did not find a relationship between patient age and increased risk of VTE. However, some studies reported increased risk in younger ALS patients compared to non-ALS controls in the same age group [17,18]. These results confirm an association between increased risk of VTE and ALS. Additionally, an increased risk of VTE occurrence was reported with disease progression and functional decline of the patient. This could be attributed to increased immobility and increased need for non-invasive ventilation, which in turn increases the risk of VTE due to their impact on blood flow in blood vessels [21–23].

The results of our meta-analysis highlight the significant risk of VTE in patients with ALS. This elevated risk emphasizes the need for proactive therapeutic interventions and careful management of VTE in ALS patients. Given the identified risk factors, such as a history of VTE, noninvasive ventilation, immobility, and decreased functional status, healthcare providers involved in the care of ALS patients should consider implementing preventive measures to reduce the occurrence of VTE. These measures may include regular monitoring for signs and symptoms of VTE, appropriate use of prophylactic anticoagulation, and patient education on the importance of maintaining mobility and managing immobility-related factors. Furthermore, healthcare professionals should be aware of the potential benefits and risks associated with anticoagulant therapy in ALS patients, considering the potential impact on disease progression and overall patient care.

This study provides the first systematic review and meta-analysis of the incidence rate and risk factors for VTE in ALS patients. The study was conducted and reported according to the guidelines for systematic reviews and meta-analyses. Several databases were searched using appropriate terms, and data extraction processes involved multiple researchers, enhancing result accuracy. However, the study faced some limitations. Sample sizes were small in some studies, as seen in Caballero 2022, Forrest 2014, and Gladman 2014. Some studies did not report results comprehensively, especially concerning subgroup and regression analyses. The included studies were predominantly from some Western countries, which limits the generalizability of the findings.

Conclusion

The incidence rate of VTE is higher in ALS patients compared to non-ALS individuals of the same age. The results showed an overall incidence rate of 22 cases per 1000 persons annually, with the risk of occurrence increasing with disease progression and deterioration in patient functional status. It is recommended to study and implement preventive measures such as anticoagulant therapy and regular monitoring measures, especially in patients with accompanying risk factors such as disease progression and a history of VTE.

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