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Original research

Venous thromboembolism risk in amyotrophic lateral sclerosis: a hospital record-linkage study

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ABSTRACT

Background Venous thromboembolism (VTE) can occur in amyotrophic lateral sclerosis (ALS) and pulmonary embolism causes death in a minority of cases. The benefits of preventing VTE must be weighed against the risks. An accurate estimate of the incidence of VTE in ALS is crucial to assessing this balance.

Methods This retrospective record-linkage cohort study derived data from the Hospital Episode Statistics database, covering admissions to England's hospitals from 1 April 2003 to 31 December 2019 and included 21 163 patients with ALS and 17 425 337 controls. Follow-up began at index admission and ended at VTE admission, death or 2 years (whichever came sooner). Adjusted HRs (aHRs) for VTE were calculated, controlling for confounders.

Results The incidence of VTE in the ALS cohort was 18.8/1000 person-years. The relative risk of VTE in ALS was significantly greater than in controls (aHR 2.7, 95% CI 2.4 to 3.0). The relative risk of VTE in patients with ALS under 65 years was five times higher than controls (aHR 5.34, 95% CI 4.6 to 6.2), and higher than that of patients over 65 years compared with controls (aHR 1.86, 95% CI 1.62 to 2.12).

Conclusions Patients with ALS are at a higher risk of developing VTE, but this is similar in magnitude to that reported in other chronic neurological conditions associated with immobility, such as multiple sclerosis, which do not routinely receive VTE prophylaxis. Those with ALS below the median age of symptom onset have a notably higher relative risk. A reappraisal of the case for routine antithrombotic therapy in those diagnosed with ALS now requires a randomised controlled trial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Venous thromboembolism (VTE) occurs more frequently in chronic neurological disorders associated with physical disability, including those with amyotrophic lateral sclerosis (ALS).
⇒ VTE is the direct cause of death in a minority of those with ALS.
⇒ Routine VTE prophylaxis is not currently recommended in ALS, but the balance of benefit versus risk depends on accurate estimates of incidence in population-based studies.

WHAT THIS STUDY ADDS

⇒ A large UK hospital record-linkage study of more than 20 000 patients with ALS demonstrated an increased risk of VTE in patients with ALS (adjusted HR (aHR) 2.7, 95% CI 2.4 to 3.0).
⇒ Patients aged under 65 had the highest relative risk (aHR 5.34, 95% CI 4.6 to 6.2).

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ The risk of VTE in ALS is significantly raised and preventable.
⇒ The case for routine VTE prophylaxis in those diagnosed with ALS is nuanced and a randomised controlled trial needs consideration.

INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder characterised by progressive muscle weakness due to the loss of motor neurons. Median survival from symptom onset is 30 months. Although the most common cause of death in ALS is respiratory muscle compromise with associated bronchopneumonia, venous thromboembolism (VTE) is recognised as a cause of sudden unexpected death.[1]

VTE comprises deep vein thrombosis (DVT) and pulmonary embolism (PE), and respectively describes the process of pathological clotting of the blood within the deep leg veins and embolisation to the pulmonary arteries. Risk factors for VTE include any disease process or environmental influence which increases blood stasis, hypercoagulability or endothelial injury (commonly known as Virchow's triad).[2] The increased risk of VTE in ALS is thought to primarily relate to reduced mobility, which exacerbates venous pooling in the lower limbs.[3] Large PEs may lead to a failure of venous return to the left heart and blood oxygenation causing cardiovascular collapse. The 30-day mortality estimates from a single DVT and PE event are 3% and 31%, respectively.[4]

PEs can also present silently—so-called 'incidental PEs'. A meta-analysis estimated the prevalence of incidental PEs, identified through CT scans across a range of comorbidities, at 2.6% (95% CI 1.9% to 2.1%).[5] Estimates for progression of silent PEs to fatal disease range from 0% to 25%.[6–8] Although conclusions from the literature are ambiguous, current consensus guidelines advise that incidental PE should be managed identically to symptomatic PE.[8] There are no studies investigating the prevalence of incidental PEs in ALS although recent work found a 2% incidence of incidental DVT in a cohort of admitted patients with ALS in Japan.[9]

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Preventing VTE is possible through mechanical (stocking or intermittent pneumatic compression) or pharmacological prophylaxis. The latter options include low molecular weight heparin (LMWH), unfractionated heparin, direct oral anticoagulants (DOACs) and aspirin.[10–13] In all cases, the risks of both occurrence and significant complications of VTE must be weighed with the risks of the prophylaxis. For pharmacological prophylaxis, this is the increased risk of bleeding events, and for mechanical prophylaxis this is the risk of skin damage through compression-related tissue ischaemia.[11]

Of the few studies of VTE in ALS specifically, the majority have been observational, small and clinic based. They have estimated yearly incidence of VTE in ALS between 2.7% and 11.2%.[1 3 14–20] This compares to an overall population rate estimate of 0.1%, which rises to 0.5% in those older than 80.[21 22] The only large population-based study reported a yearly VTE incidence of 2% in a cohort of 4205 patients with ALS for a US health insurance claims database.[23]

Through access to a large observational, retrospective cohort of hospital record-linkage data from the National Health Service (NHS) in England, we aimed to characterise both the incidence of VTE in ALS and the relative risk of VTE in ALS compared with a reference cohort of hospital controls.

METHODS

Data sources and study population

A data extract was derived from the English National Hospital Episode Statistics Admitted Patient Care (HES-APC) database with linkage to national mortality civil registrations under data access agreement reference DARS-NIC-315419-F3W7K. The database is estimated to contain 98%–99% of hospital activity in England (around 20 million episodes per year).[24] The data extract used in this study comprised all HES-APC and mortality records belonging to three categories of patients: (1) those admitted to NHS hospitals between 1 April 2003 and 31 December 2019 with a record of ALS (ICD10 G12.2) coded as the primary diagnosis, hereafter termed the 'ALS cohort'; (2) those admitted during the same time period with one of the diagnoses or procedures listed as the primary cause of admission, hereafter termed the reference cohort* and (3) those who had a VTE (ICD10 I26, I80–I82) coded in any diagnostic position on a HES-APC record or, if relevant, their death record during the same time period, irrespective of whether they were also included in (1) or (2).

*The reference cohort comprised 17 425 337 individuals admitted to hospital for vasectomy, cataract treatment, single delivery, upper respiratory tract infections, inguinal hernia, gallstones, nasal polyps, deflected septum, bunions, limb fractures, dislocations/sprains/strains, teeth disorders, otitis, haemorrhoids, nail disorders, sebaceous cyst, knee internal derangement, bruising, appendectomy, dilation and currettage, tonsillectomy, hip replacement, knee replacement, tendency to fall, urinary tract infection. The reference cohort was designed to be as representative as possible of the general population in terms of general health status by selecting a diverse range of conditions that are common and relatively minor. Herbert *et al* provide further information and discussion on the design and utility of the HES-APC.[24]

Study design

The study design was a retrospective cohort study. Each patient's cohort entry date was the discharge date of their index admission, which for the ALS cohort was the patient's earliest known admission for ALS coded as the primary diagnosis, and for the reference cohort was the patient's earliest known admission for one of the reference conditions . The patients in each cohort were then 'followed up' through record linkage for any subsequent admission up to 2 years later where VTE was coded in any diagnostic position. The null hypothesis was that the incidence of VTE would be the same in both cohorts.

Statistical analysis

Patients in each cohort were followed for up to 2 years from the date of cohort entry until the date of first known VTE diagnosis, death or the end of the follow-up period (31 December 2019), whichever came first. Age-sex-specific annual incidence rates of VTE hospitalisation in each cohort were calculated per 1000 person-years (censoring for death). Multivariable Cox proportional hazards regression models were used to estimate the adjusted HRs (aHR) of VTE in the ALS cohort compared with the reference cohort, with adjustment for age (in 5-year groups), sex, year of index admission, region of residence (nine NHS regions), patients' Index of Multiple Deprivation score in quintiles, ethnic category, and Charlson Comorbidity Score. It was not possible to include smoking and body mass index as they are not routinely recorded in the HES-APC. Individual-level prescribing data was not available. Time from cohort entry was used as the underlying time variable.

To examine the representativeness of the reference cohort compared with the general population in relation to VTE risk, we compared the age-sex-specific rates of annual incidence of VTE hospitalisation in the reference cohort with the 'true' annual incidence of VTE hospitalisation in the English population. The latter was calculated by ascertaining the age-sex specific counts of VTE hospitalisation in each calendar year of national HES and dividing these by the corresponding English national age-sex-specific mid-year population denominators in each calendar year (obtained from the national Office for National Statistics), and then multiplying by 1000. These rates were then compared with the age-sex-specific rates of VTE in the reference cohort as calculated in the longitudinal analysis. To explore the possibility that recent discharge from hospital might itself be associated with an elevated risk of VTE in early follow-up, follow-up in the reference cohort was divided into four 6-month periods (0–6 months, 6–12 months, 12–18 months and 18–24 months), and the incidence of VTE per 1000 person-years in each period separately was then compared with the true incidence of VTE in the general population. The actual general population was not used as the reference population because the national population denominators were aggregated by age and sex only, whereas the cohort of hospital controls enabled greater internal validity, multivariable adjustment and flexibility in the analysis of follow-up time.

RESULTS

The ALS and reference cohorts comprised, respectively, 21 163 and 17 425 337 individuals. Figure 1 summarises the age–sex distribution of the ALS cohort. The mean age of patients in the ALS cohort was 68 years (SD 12.2).

Figure 2 compares the age-sex-specific incidence of VTE in the reference cohort (by time since index admission) with that of the general population: in the first 6 months of follow-up, incidence of VTE in the reference cohort was substantially higher than in the general population; thereafter, incidence of VTE in the reference cohort closely resembled that of the true general population. Thus, the reference cohort after the first 6 months of follow-up could be regarded as validly equivalent to the 'general

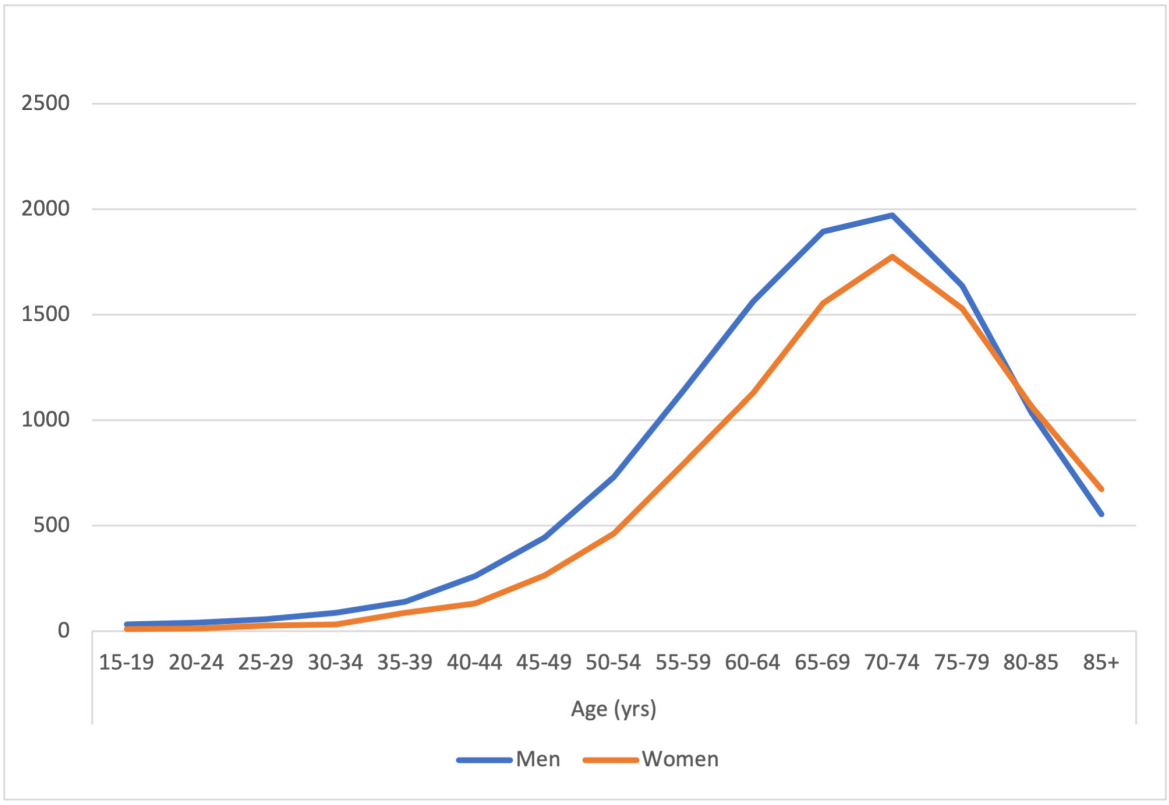

Figure 1 Age–sex distribution of patients included in the ALS cohort. ALS, amyotrophic lateral sclerosis.

population' in terms of background risk of VTE, with the first 6 months of follow-up representing a short-term additional risk conferred by recent hospitalisation.

The overall incidence of VTE in the ALS cohort was 18.8 per 1000 person-years. After multivariable adjustment, the overall incidence of VTE in the ALS cohort was nearly three times higher than in the reference cohort (aHR 2.7, 95% CI 2.4 to 3.0) . There was a significantly increased risk of both PE (315 cases observed; aHR 3.4, 95% CI 3.0 to 3.9) and DVT (232 cases observed; aHR 2.2, 95% CI 1.9 to 2.5). Figure 3 shows the absolute incidence rates of VTE in the ALS cohort (unadjusted) and aHRs, stratified by sex, age group (<65 and 65+ years) and follow-up period (0–6 months, 6–24 months). While the absolute incidence of VTE in the ALS cohort was similar

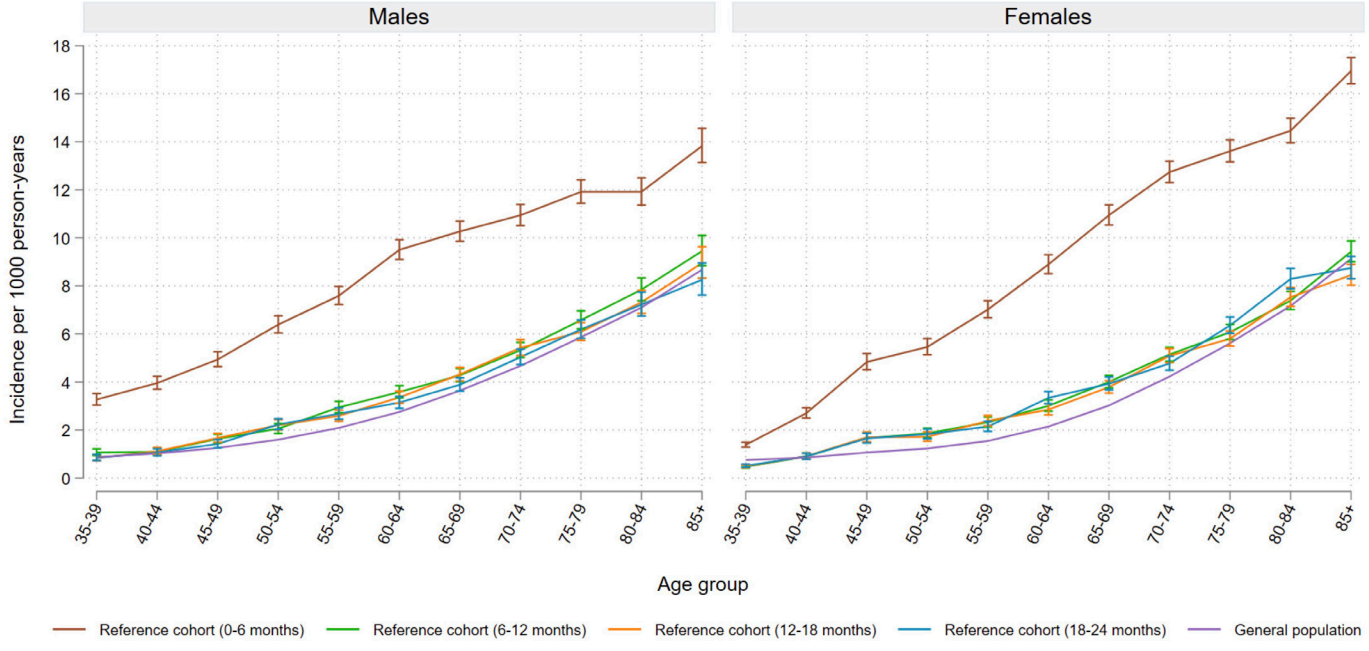

Figure 2 Annual incidence of hospital recorded VTE in England: reference cohort (by time since index admission) versus general population. VTE, venous thromboembolism.

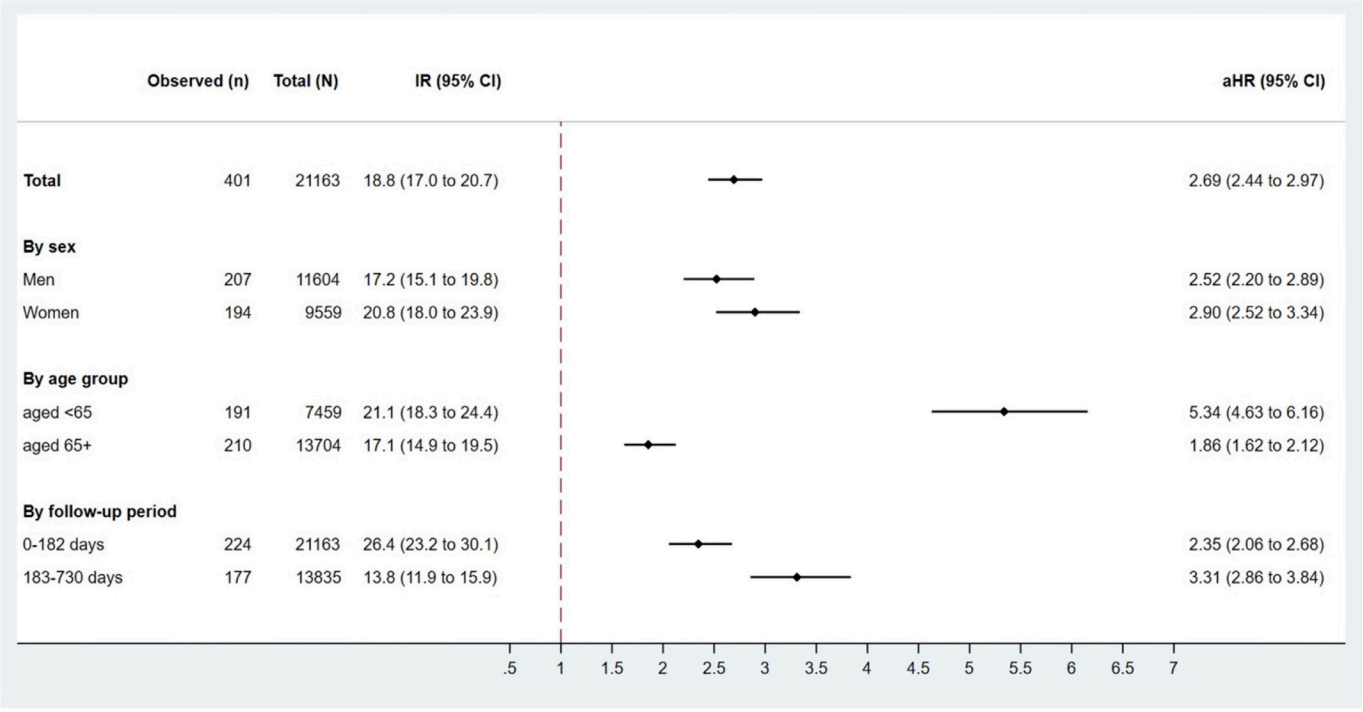

Figure 3 Forest plot showing adjusted HR for VTE in ALS by patient group. aHR, adjusted HR; ALS, amyotrophic lateral sclerosis; IR, incidence rate; VTE, venous thromboembolism.

in older patients (aged 65+) and younger patients (aged <65), the aHR was significantly higher in younger patients than older patients (likelihood ratio test for heterogeneity χ^2 (1)=104.6; p<0.0001). The aHR was significantly higher in months 6–24 of follow-up than in the first 6 months (likelihood ratio test for heterogeneity χ^2 (1)=11.5; p=0.0007).

DISCUSSION

This large population-based study showed that the risk of VTE in the ALS cohort of patients was nearly three times higher than the reference cohort after multivariable adjustment. The higher aHR in younger patients with ALS, and in later periods of follow-up, suggest that ALS directly influences risk of VTE, independently of biological ageing and recent hospitalisation. This might relate to the slower rate of disease progression and tendency to limb predominance in younger patients with the consequence of prolonged immobility.[25] An alternative explanation might be that the background prevalence of immobility (and therefore VTE risk) is so low in the younger general population, that ALS (and therefore immobility) disproportionately increases VTE risk in such age groups. Another large record-linkage study reported a similar risk to our overall estimate (HR 3.3, 95% CI 2.6 to 4.0) and a similar yearly incidence of 2%.[26] Multiple previous smaller studies comparably found an increased incidence of VTE in ALS.[1 3 14–18] Some of these studies have identified significant phenotype risk differences. Most notably, lower-limb-dominated patients with ALS showed an annual VTE incidence as high as 35%.[3 16] A summary of published literature is in table 1. This study also found that in patients with ALS the relative risk of PE was higher than that of DVT (aHR 3.4 vs 2.2). One reason for this might be that DVT is more susceptible than PE to underdetection and lower hospital presentation rates in patients with ALS, in which case the relative risk of DVT could be underestimated.

It is likely that primary VTE prophylaxis in ALS is currently avoided due to ambiguity over the precise balance of risks associated with such therapy, rather than the existence of conclusive evidence proving its disproportionate excess harm. There is a distinct lack of high-quality randomised control trials assessing this balance of risks in neurological diseases. It is unlikely that the ALS disease process itself increases coagulability, but rather the associated immobility. Immobile individuals who receive regular VTE prophylaxis include those acutely poststroke (21-day VTE risk of 40%) and spinal cord injury (36 month VTE risk of 23.4%).[27 28] However, conditions with comparable VTE risk to ALS such as multiple sclerosis (aHR 2.56 (95% CI 2.06 to 3.20) and cancer (aHR 4.7 (95% CI 4.5 to 4.9), do not routinely receive routine VTE prophylaxis.[29–31] An exception is patients with multiple myeloma on prothrombotic chemotherapy such as lenalidomide, whose yearly risk of VTE without prophylaxis is 12% and is reduced to 2.3% with low-dose aspirin therapy.[32] Aspirin is also effective as prophylaxis in postsurgical patients.[33] If pharmacological prophylaxis were adopted in ALS, aspirin may represent a safer drug candidate due to its minimal effect on the risk of serious bleeding events such as cerebral or gastrointestinal haemorrhage (RR 1.4 95% CI 1.2 to 1.7).[34] Graduated compression stockings represent a mechanical alternative, however high-quality evidence proving their efficacy is limited only to hospitalised surgical patients and their long-term use carries potential for harm, causing skin breakdown in up to approximately 4%.[35–38] Intermittent pneumatic compression has been shown to be highly effective in critically ill and stroke patients but would likely prove impractical for many patients with ALS who retain residual mobility as these devices require large motors to cyclically inflate compression cuffs.[39–41]

Routine practice in the UK dictates that nearly all hospital inpatients over 65, even without the presence of pathology, are given low-dose anticoagulation (typically LMWH) to reduce

Table 1 Summary of VTE in ALS literature

Authors	DOI/access	Year	Study description	Follow-up (years)	No of patients	% death by PE	% unidentified sudden death	Incidence of VTE
Barnabe *et al*[20]	10.1016/j.rpth.2023.102287	2023	Prospective cohort study of 227 patients at a French hospital with a median follow-up of 717 days.	2	227	0	0	2.93% annual
Takeda *et al*[9]	10.1016/j.jns.2024.122896	2023	Prospective cohort study investigating the incidence of incidental DVT in 65 patients with ALS.	n/a	65	N/A	N/A	2% incidental DVT annual
Kupelian *et al*[23]	10.1212/CPJ.0000000000200110	2023	Retrospective observational study over 10 years comparing the number of VTE-related claims in 4205 patients with ALS and 21 025 controls using a US health insurance claims database.	10	4205	N/A	N/A	1.99% annual
Caballero-Eraso *et al*[19]	10.1016/j.thromres.2022.01.002	2022	Prospective cohort study following 44 patients for 2 years	2	44	N/A	N/A	8.5% annual
Mira Padilla *et al*[15]	10.1183/13993003.congress-2021.PA3584	2021	Retrospective observational study with 218 patients with ALS in Spain	10	218	1	N/A	3.9% in 10 years
Forrest *et al*[16]	10.3109/21678421.2014.984724	2015	Audit of 130 patients with ALS followed up over 12 months in an Australian clinic	1	130	0	N/A	3.75% annual (for PE)
Gladman *et al*[3]	10.1212/WNL.0000000000000405	2014	Prospective study of 50 patients in a Canadian clinic followed up for clinically important VTE for 1 year	1	50	0	0	11.2% annual incidence (36% and 36% for leg-onset or leg weakness)
Gil *et al*[14]	10.1111/j.1468–1331.2008.02307.x	2008	Prospective follow-up study of 302 patients with ALS in France investigating cause of death via patient records and attending physicians	1	302	2	0.7	N/A
Corcia *et al*[1]	10.1080/17482960701656940	2008	Postmortem study on cohort of 100 patients with ALS in France investigating cause of death	N/A	100	6	N/A	N/A
Qureshi *et al*[18]	10.1212/01.wnl.0000250444.30622.ee	2007	DVT in patients with ALS in 2 clinical trials in the USA	N/A	501	N/A	N/A	2.7% annual (for DVT)
Elman *et al*[17]	10.1080/14660820510043226	2005	Audit of 438 patients with ALS over 4 years	4	438	N/A	N/A	3.3% annual (for VTE)

ALS, amyotrophic lateral sclerosis; DVT, deep vein thrombosis; N/A, not available; VTE, venous thromboembolism.

the risk of VTE.[13] The American College of Chest Physicians acknowledge that it is likely that immobile care-home patients have similar VTE risk to postacute care patients, but these patients are rarely given prophylaxis.[11] The reason for this is the high risk of bleeding, particularly intracranially, from falls when taking anticoagulants. Between 1% and 7% of patients per year receiving prophylactic dose of the DOAC apixaban experience significant bleeding events.[42] ALS is a condition associated with a high risk of falls, despite efforts to minimise their frequency using predictive calculators, and most clinicians do not institute routine anticoagulant or mechanical VTE prophylaxis.[43] One possible strategy could be to instigate pharmacological prophylaxis only in wheelchair-dependent patients at lower risk of falls.

One potential weakness of this study is that the hospital record database only included those admitted to hospital at some point in their disease course and not all patients diagnosed with ALS. It is, therefore, possible that those with ALS in this study had an inherently higher VTE risk than non-hospitalised individuals with ALS, for example, due to the presence of VTE inducing comorbidities precipitating admission. However, a study in Italy reported that 98% of patients with ALS are admitted to hospital at least once in their disease course.[44] We also mitigated this bias by calculating aHRs against a matched cohort of hospitalised patients, who were likely to have a similar level of inherent VTE risk (minus that caused by ALS). Therefore, our aHR result is felt to be generalisable to the majority of those with ALS in the UK. This study did not directly compare ALS with other causes of progressive paralysis. It is, therefore, possible that the increased risk of VTE seen in ALS might also be true of any other cause of paralysis. It was not possible to manually recheck coded diagnoses from the HES-APC as these data were not available. However, a meta-analysis investigating coding accuracy from 2004 to 2011 in this database estimated accuracy at 96.2% for primary diagnoses (the same diagnostic position used for this study). Furthermore, it is unlikely that an ALS diagnosis would be made lightly owing to its severity and rarity. Due to the limitations of record linkage, we were unable to investigate the previously reported, and intuitively plausible, increased risk factor of lower limb weakness in ALS as well as other specific ALS patient groups such as bulbar-onset and percutaneous gastrostomy-fed patients. Detailed phenotypic and staging information on patients with ALS was also not available. We were also unable to investigate the prevalence of incidental PE in this patient group, which requires further dedicated work.

Alongside our novel finding of higher risk in younger people hospitalised with ALS, this study suggests a more individualised balance of risks and benefits may need to be defined to minimise the rare, but potentially catastrophic complication of PE in ALS. It strengthens the case for a definitive randomised trial of routine VTE prophylaxis after a diagnosis of ALS, possibly comparing antithrombotic therapy, against either compression stockings or no intervention. If antithrombotic therapy reduced the risk of DVT by 80%, we estimate there would need to be 12 events and approximately 650 person-years of follow-up (alpha 0.05 and 80% power), so a multicentre study would be required.

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