

How Amyotrophic Lateral Sclerosis Contributes to Increased Venous Thromboembolism Risk

Dear Editor,

We are grateful for the interest shown by [Authors] in our study and for their thoughtful comments, which raise important points about venous thromboembolism (VTE) risk in amyotrophic lateral sclerosis (ALS) patients [1]. Below, we address their concerns in detail:

1. Dependency on Mobility and Heparin Prophylaxis:

Immobility was indeed identified as a key risk factor for VTE in ALS patients [2]. However, the included studies did not provide detailed data on prophylactic anticoagulation regimens. Notably, some studies excluded patients on anticoagulant therapy (e.g., Caballero-Eraso and Gladman) as their primary aim was to assess the baseline risk of VTE in ALS patients, with anticoagulant use potentially confounding this relationship. Nevertheless, anticoagulant prophylaxis in ALS patients with additional risk factors warrants further investigation.

2. Exclusion of Coagulation Disorders: Our analysis was limited by the data reported in the included studies, which did not systematically assess or exclude pre-existing coagulopathies. We acknowledge this limitation and agree that future research should explore the interplay between coagulation abnormalities and ALS, particularly to differentiate primary ALS-related VTE risk from other underlying conditions.

3. Role of Infection: Infections are a recognized risk factor for VTE, and ALS patients, particularly those with respiratory compromise, are prone to bronchopulmonary infections. However, data on acute infections were inconsistently reported in the included studies. Future research should aim to account for the influence of infections on VTE risk to provide a more comprehensive understanding.

4. Relation to Disease Severity: Disease severity is a critical determinant of VTE risk, as evidenced by our findings linking non-invasive ventilation, immobility, wheelchair dependence, and functional decline with higher VTE rates [2]. Each of these risk factors is closely tied to disease progression, underscoring the importance of considering severity in assessing VTE risk.

5. Variability Between Studies: Heterogeneity in VTE incidence rates likely reflects differences in study populations and methodologies. However, small sample sizes are likely the primary contributor to variability. As noted in our meta-analysis, studies with larger sample sizes (e.g., Goldacre and Kupelian) reported similar incidence rates, reinforcing the importance of robust sample sizes for accurate incidence estimates.

Additionally, we performed sensitivity analyses to address variability. Future studies should prioritize larger cohorts and standardized methodologies to enhance reliability.

6. Rate of Pulmonary Embolism (PE): We appreciate the authors highlighting the significance of PE, which is frequently reported as a cause of death in ALS patients. Seven studies in our meta-analysis reported PE separately, accounting for 385 symptomatic PE cases or PE associated with DVT out of 26,307 patients. These findings emphasize the need for vigilant monitoring and early intervention to mitigate PE-related mortality in ALS.

Mechanisms Linking ALS to Increased Risk of Venous Thromboembolism

To expand on the risk of venous thromboembolism (VTE) in patients with amyotrophic lateral sclerosis (ALS), I would like to summarize the factors that may contribute to this increased risk. VTE risk is notably elevated in patients with ALS, primarily due to factors associated with the disease's progression [2]. While the direct contribution of ALS pathophysiology to coagulability is uncertain and not yet proven, reduced mobility remains the most significant and well-documented contributing factor [3]. ALS leads to progressive muscle weakness and paralysis, reducing physical activity and slowing venous blood flow, particularly in the lower extremities. This venous stasis—a key component of Virchow's triad—is exacerbated in advanced stages by mechanical ventilation or prolonged bed rest.

Additionally, ALS is associated with chronic systemic inflammation, evidenced by elevated inflammatory markers [4]. Inflammation can activate endothelial cells, platelets, and the coagulation cascade, promoting a prothrombotic state [5]. However, the specific mechanisms linking systemic inflammation to VTE in ALS, including potential alterations in coagulation status, remain poorly understood and warrant further investigation. Endothelial dysfunction, observed in ALS and other neurodegenerative diseases, may also play a role and should be evaluated [6].

Comorbidities commonly seen in ALS patients further compound the risk of VTE. These include respiratory infections and cardiovascular complications, with acute infections particularly exacerbating inflammation.

Conclusion

The progression of ALS significantly increases the risk of VTE and pulmonary embolism (PE) through a combination of reduced mobility, comorbidities such as infections or cardiovascular complications, and potentially systemic inflammation and endothelial dysfunction. Although

current guidelines for ALS do not include VTE prophylaxis, addressing these risks requires effective preventive strategies, which future research should explore. Early mobilization within the patient's functional limits can reduce venous stasis, while graduated compression stockings or pneumatic compression devices may improve venous return in immobile patients. For those at high risk, particularly those who are immobile or hospitalized, prophylactic anticoagulation or antiplatelet therapy should be considered with careful assessment of bleeding risks. Vigilant monitoring for symptoms of deep vein thrombosis or PE, such as leg swelling, pain, or unexplained shortness of breath, is critical for timely diagnosis and intervention. While these measures hold promise, further research is essential to refine these strategies and mitigate the burden of VTE in ALS patients effectively.

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