# Response to Comment on: Multimorbidity, comorbidity, frailty, and venous thromboembolism

We thank Dr. Zervou and Dr. Goulielmos for their interest in our article in Haematologica on the role of multimorbidity, comorbidity and frailty in the development of venous thromboembolism (VTE).[1,2] We agree that autoimmune diseases may deserve further attention among VTE comorbidities.[1] In the published review we focused on the association between VTE and multimorbidity, comorbidity, and frailty in general. However, several autoimmune diseases are associated with a higher risk of VTE.[3] Many autoimmune diseases also share genetics and pathogenesis.[4] In Sweden multimorbidity of autoimmune connective tissue disorders, psoriasis, thyroid disorders and osteoporosis clusters in families and are associated with VTE.[5-7] Osteoporosis is not considered an autoimmune disease but the clustering of osteoporosis together with several autoimmune diseases might be related to corticosteroid treatment. It could be of great interest as suggested by Dr. Zervou and Dr. Goulielmos to further study the clustering and shared genetics of autoimmune disorders and relation to VTE.[1]

The interplay between coagulation and immune system is believed to be an early evolutionary phenomenon in response to infection.[8] It is suggested that the coagulation and immune systems originated from one system present in early life forms.[8] In simple organisms hemocytes can carry out both immune response and coagulation processes.[8] Evolution led to the separation of the coagulation and immune functions in higher organisms.[8] Moreover, the major proteolytic cascades in the blood, complement and coagulation pathways, share a common evolutionary ancestor.[9] Delineating the multiple cross-talk between immune response and coagulation processes may uncover novel disease mechanisms and therapeutic insights.[9] A recent example is the observation that hereditary angioedema caused by C1 inhibitor (C1-INH) protein deficiency is associated with increased risk of VTE.[10] C1-INH is a multifunctional plasma serine protease inhibitor that negatively regulates components of the kallikrein-kinin, contact, and complement systems, including plasma kallikrein, activated factor XII, activated Factor XI, complement C1 components, and mannose-associated serine protease (MASP) 1 and 2.[10] Congenital C1-INH deficiency (type I) or dysfunction (type II) is associated with hereditary angioedema (HAE), a rare disorder characterized by episodes of cutaneous and submucosal swelling.[10] However, due to the cross-talk between the coagulation and complement system HAE patients with C1-INH deficiency have increased plasma levels of markers of activation of coagulation and increased risk for VTE.[10]

In conclusion, as suggested by Dr. Zervou and Dr. Goulielmos the recognition of the potential association between various autoimmune diseases and VTE may lead to novel discoveries.[1] Autoimmune diseases may deserve special attention among VTE comorbidities, which may result in novel and improved ways to prevent and treat VTE and autoimmune diseases.

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https://doi.org/10.3324/haematol.2025.287469

Received: January 27, 2025.
Accepted: January 30, 2025.
Early view: February 6, 2025.



**Disclosures**

No conflicts of interest to disclose.

**Contributions**

BZ wrote the first draft and JMC and BZ revised the article and approved the final version.

**Funding**

Funding by the ALF-funding from Region Skåne and the Swedish Research Council (2020-01824).

## References

1. Zervou MI, Goulielmos GN. Comment on: Multimorbidity, comorbidity, frailty, and venous thromboembolism. Haematologica. 2025;110(10):2548-2549.
2. Zöller B, Connors JM. Multimorbidity, comorbidity, frailty, and

venous thromboembolism. Haematologica. 2024;109(12):3852-3859.
3. Menichelli D, Cormaci VM, Marucci S, et al. Risk of venous thromboembolism in autoimmune diseases: a comprehensive review. Autoimmun Rev. 2023;22(11):103447.
4. Zhernakova A, Withoff S, Wijmenga C. Clinical implications of shared genetics and pathogenesis in autoimmune diseases. Nat Rev Endocrinol. 2013;9(11):646-659.
5. Zöller B, Pirouzifard M, Holmquist B, Sundquist J, Halling A, Sundquist K. Familial aggregation of multimorbidity in Sweden: national explorative family study. BMJ Med. 2023;2(1):e000070.
6. Ahrén J, Pirouzifard M, Holmquist B, Sundquist J, Sundquist K, Zöller B. Multimorbidity disease clusters are associated with venous thromboembolism: an extended cross-sectional national study. J Thromb Thrombolysis. 2024;57(6):898-906.
7. Ahrén J, Pirouzifard M, Holmquist B, Sundquist J, Sundquist K, Zöller B. Multimorbidity is associated with risk of incident venous thromboembolism - a nationwide proof-of-concept study. Thromb. Update. 2025;18:100198
8. Arneth B. Coevolution of the coagulation and immune systems. Inflamm Res. 2019;68(2):117-123.
9. Conway EM. Reincarnation of ancient links between coagulation and complement. J Thromb Haemost. 2015;13(Suppl 1):S121-S32.
10. Sundler Björkman L, Pirouzifard M, Grover SP, et al. Increased risk of venous thromboembolism in young and middle-aged individuals with hereditary angioedema: a family study. Blood. 2024;144(4):435-444.