Fit, unfit, or frail? Now easier to tell for Hodgkin lymphoma

Alison J. Moskowitz

Lymphoma Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence: A. J. Moskowitz
moskowia@mskcc.org

Received: June 25, 2025.
Accepted: July 4, 2025.
Early view: July 17, 2025.

https://doi.org/10.3324/haematol.2025.288033

In the article, "A simplified frailty score predicts outcome in curatively treated older patients with classical Hodgkin lymphoma", Lia and colleagues describe a simplified index for stratifying older (aged ≥60 years) Hodgkin lymphoma (HL) patients as fit, unfit, or frail.[1] This score can easily be incorporated into routine practice, potentially identifies patients suitable for palliative therapy, and provides a platform for future studies.

Hodgkin lymphoma is rare and disproportionately impacts young patients; therefore, developing optimal therapy for older patients is challenging. Older HL patients historically experience less favorable outcomes, primarily due to poor treatment tolerability.[2] Frailty assessments have the potential to risk stratify patients and ultimately improve outcomes by enabling personalized therapy. Up until now, there was no specific tool for HL patients. Lia and colleagues succeeded in creating a user-friendly tool that can potentially aid in guiding treatment choices.

Lia *et al.* developed their score using the Cancer Registry of Norway which included 279 HL patients, aged ≥60 years, treated with curative intent from 2000-2015. Three factors were found to be predictive of progression-free survival (PFS) by multivariate analysis (MVA): age (≥70 years), Eastern Cooperative Oncology Group Performance Status (ECOG PS) ≥2, and comorbidity score (cumulative illness scale for geriatrics [CIRS-G]) ≥8. Similarly, age and comorbidity score were predictive of overall survival (OS) by MVA, while ECOG PS was not predictive. The three factors were developed into a score that stratified patients as fit (0 factors), unfit (1-2 factors), or frail (3 factors). The score was then validated using the Swedish Lymphoma Register which included 792 HL patients aged ≥60 years treated from 2000-2015. Importantly, in the validation set, comorbidities were assessed using the simpler Charlson Comorbidity Index (CCI), rather than the CIRS-G, demonstrating that the frailty score can be generalized for either comorbidity index.

Treatment of HL patients aged ≥60 years has evolved over the last few decades and outcomes appear to be improving significantly. Historically, outcomes were poor, as demonstrated by the North American Intergroup E2496 study, which showed significantly inferior outcomes for patients aged ≥60 years treated with standard anthracycline-based therapy, such as doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD).[2] High rates of bleomycin toxicity (43%) and unacceptable rates of treatment-related mortality (TRM) (9%) contributed to these poor outcomes.[2] The ECHELON-1 study showed that brentuximab vedotin (BV) plus doxorubicin, vinblastine, and darcarbazine (BV-AVD) was superior to ABVD for advanced-stage disease; however, this did not hold true for patients aged ≥60 years who experienced 5-year PFS of 67% compared to 84% for younger patients. Again, less favorable outcomes were likely related to higher rates of TRM (4%) and toxicities such as neutropenic fever (37%).[3] BV and AVD were subsequently studied using an alternative schedule for patients aged ≥60 years, with single-agent BV for 2 cycles followed by AVD for 6 cycles and then another 4 cycles of BV ("sequential BV-AVD").[4] This sequential regimen turned out to be more efficacious, with 2-year PFS of 84%, likely due to lower rates of treatment-related toxicity, such as neutropenic fever (8%).[4] More recently, nivolumab plus AVD (N-AVD) was shown to be more efficacious than BV-AVD for advanced stage disease, and for the first time, this regimen was equally efficacious for older patients as for younger patients (2-year PFS 89% *vs*. 93%, respectively).[5,6] Furthermore, a phase II study of N-AVD for patients aged ≥60 years showed no impact of geriatric impairments on PFS or treatment-related toxicity; however, no patients enrolled would have been classified as frail by the Lia *et al.* score.[7]

The score developed by Lia *et al.* is helpful for identifying patients suitable for curative therapy. Based on the data from the Cancer Registry of Norway, treating with curative approaches is justified for fit and unfit patients as these patients had 5-year PFS of 74% and 49%, respectively. Fur-

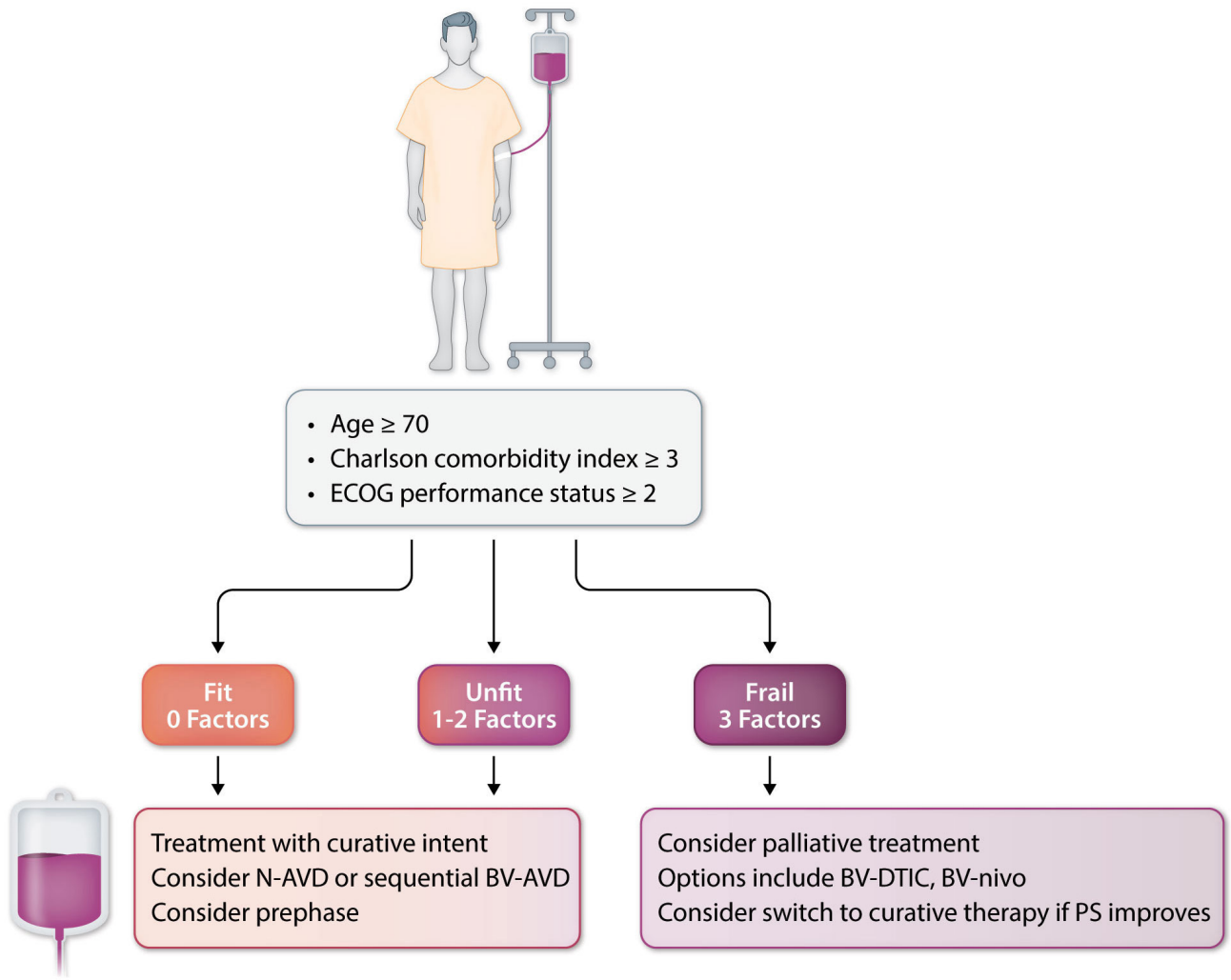

Figure 1. A simplified frailty score for older patients with Hodgkin lymphoma. Three factors (age, comorbidity index, and performance status) stratify patients as fit (0 Factors), unfit (1-2 Factors), or frail (3 Factors). Fit and unfit patients should be considered for treatment with curative intent. Frail patients would benefit from starting with palliative therapy. BV-AVD: brentuximab vedotin, adriamycin, vinblastine, dacarbazine; BV-DTIC: brentuximab vedotin, dacarbazine; BV-nivo: brentuximab vedotin, nivolumab; N-AVD: nivolumab, adriamycin, vinblastine, dacarbazine; ECOG: Eastern Cooperative Oncology Group; PS: performance status.

thermore, it is likely important to preserve dose intensity since unfit patients had improved outcomes if they received at least 80% of standard dose of doxorubicin with cycle 1. In contrast, Lia and colleagues showed that frail patients have very poor outcomes when treated by curative intent: 5-year PFS and OS were only 11% and 22%, respectively, in the training set, and 4% and 0%, respectively, in the validation set. This suggests that frail patients should be considered for palliative approaches. BV was evaluated in combination with dacarbazine (BV-DTIC) or nivolumab (BV-nivo) in a phase II study for older patients unfit for conventional chemotherapy.[8] Complete response rates for the two regimens were high at 64% and 67%, respectively, for BV-DTIC and BV-nivo. Furthermore, responses were durable with median PFS of 47.2 months for BV-DTIC and not reached for BV-nivo.[8] Starting with regimens such as BV-DTIC or BV-nivo is reasonable for frail patients. These could serve as stand-alone therapies or potentially aid in improving performance status and in providing bridging to curative therapy such as N-AVD (Figure 1).

Moving forward, it is important to validate the Lia *et al.* score in prospective clinical trials and to assess its efficacy with novel regimens such as sequential BV-AVD and N-AVD. Plans are already underway to validate the score in a prospective registry in Scandinavia. Given the simplicity of the score, it should be possible to retrospectively evaluate it in completed prospective studies and incorporate it into clinical practice.

Disclosures

AJM has received research grants from Affimed, Bristol-Myers Squibb, Incyte, Merck, Pfizer, and SecuraBio. She is a consultant for Affimed, Astra Zeneca, Bio Ascend, Merck, Pfizer, Takeda, and Tessa Therapeutics.

References

1. Lia K, Jørgensen RRK, Wikman P, et al. A simplified frailty score predicts outcome in curatively treated older patients with classical Hodgkin lymphoma. Haematologica. 2025;110(10):2356-2366.
2. Evens AM, Hong F, Gordon LI, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford

V in older Hodgkin lymphoma patients: a comprehensive analysis from the North American intergroup trial E2496. Br J Haematol. 2013;161(1):76-86.
3. Evens AM, Connors JM, Younes A, et al. Older patients (aged ≥60 years) with previously untreated advanced-stage classical Hodgkin lymphoma: a detailed analysis from the phase III ECHELON-1 study. Haematologica. 2022;107(5):1086-1094.
4. Evens AM, Advani RH, Helenowski IB, et al. Multicenter phase II study of sequential brentuximab vedotin and doxorubicin, vinblastine, and dacarbazine chemotherapy for older patients with untreated classical Hodgkin lymphoma. J Clin Oncol. 2018;36(30):3015-3022.
5. Rutherford SC, Li H, Herrera AF, et al: Nivolumab-AVD versus brentuximab vedotin-AVD in older patients with advanced-stage classic Hodgkin lymphoma enrolled on S1826. J Clin Oncol. 2025 Jun 16:JCO2500204. doi: 10.1200/JCO-25-00204. [Epub ahead of print]
6. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in advanced-stage classic Hodgkin's lymphoma. N Engl J Med. 2024;391(15):1379-1389.
7. Torka P, Feldman T, Savage KJ, et al. Phase II trial of nivolumab plus doxorubicin, vinblastine, dacarbazine as frontline therapy in older adults with Hodgkin lymphoma. J Clin Oncol. 2025;43(8):985-993.
8. Friedberg JW, Bordoni R, Patel-Donnelly D, et al. Brentuximab vedotin with dacarbazine or nivolumab as frontline cHL therapy for older patients ineligible for chemotherapy. Blood. 2024;143(9):786-795.