When 'simplified' may be oversimplified: reassessing frailty scoring in elderly Hodgkin lymphoma. Comment on: "A simplified frailty score predicts outcome in curatively treated older patients with classical Hodgkin lymphoma"

We read with great interest the recent report by Lia *et al*. on a simplified frailty index to predict outcomes in older patients with classical Hodgkin lymphoma (cHL) treated with curative-intent regimens.[1] This effort to stratify fitness using readily available clinical data is timely. However, we identify several important limitations that were not fully acknowledged, and which may affect the generalizability and clinical applicability of the proposed score.

First, the cohort definition and selection introduce bias. The study included only patients aged ≥60 years who received "curative" therapy, defined as any typical HL regimen with ≥50% standard doxorubicin in the first cycle. By this criterion, the frailest patients are systematically excluded, for example those too unwell to receive anthracycline or any chemotherapy. In Lia's other population-based analysis, patients with curative therapy (median age 69 years) were significantly younger, had better performance status, were fully independent in activities of daily living (ADL), and had fewer comorbidities than those receiving palliative care.[2] Indeed, the palliatively treated elderly cohort had a median age of 81 years (range, 61-94), whereas the curative group's median was only 69 years (range, 60-90). In short, the frailest elderly (e.g. octogenarians and non-agenarians) - often the very target of frailty assessment – were not represented. This selection bias likely overestimates outcomes in the "unfit" group and limits the score's applicability to the broader elderly HL population. For example, Lia *et al*. report a 5-year overall survival (OS) of 52% in the "unfit" group (score 1-2), but this does not include those excluded from curative therapy who might have far worse survival. To address this, we recommend that future work incorporate all older HL patients, regardless of treatment received, or at least analyze the excluded groups. Population-based series of elderly HL (including palliative cohorts) could be used to validate or calibrate a frailty model. Competing-risk methods should be employed to account for high non-HL mortality in this population (see below). In prospective studies, enrolling all patients ≥60 years old at diagnosis - even if only observation or palliative care is given - would yield a frailty index that truly spans the spectrum from very fit to very frail. In short, the score should be tested in a cohort that reflects real-world clinical diversity, not only the subset who tolerated ≥50% doxorubicin from the outset.

Second, the frailty variables themselves are incomplete. By construction, the simplified index uses only age (≥70 years), Eastern Cooperative Oncology Group (ECOG) performance status (≥2), and Cumulative Illness Rating Scale (CIRS-G) (≥8). While these are plausible markers, they capture only a portion of true geriatric vulnerability. Notably absent are measures of functional independence (instrumental ADL [IADL]), cognition, nutrition, and other geriatric syndromes. A recent systematic review in hematologic malignancies showed that impairments in polypharmacy, nutritional status, and IADL are very common in older patients - even those with "good" World Health Organization performance status (WHO PS) - and that these impairments predict survival independent of ECOG.[3] In that review, ECOG (WHO PS) lost prognostic value once formal geriatric deficits were accounted for. Similarly, prospective geriatric oncology studies show that objective assessment of ADL, cognitive screening, and nutritional indices refine risk stratification beyond PS. For example, Kathrine *et al*. developed an analogous frailty score in older diffuse large B-cell lymphoma where the model ultimately included ADL-dependency, Charlson comorbidity, a geriatric nutritional index (GNRI), and age ≥85 years.[4] This underscores that ADL and nutrition are strong predictors. Likewise, Stauder *et al*. found that malnutrition (weight loss, low albumin, GNRI) was an independent adverse prognostic factor in older hematologic cancers.[5] In contrast, Lia *et al*.'s index omits nutrition entirely and could not reliably incorporate ADL (they note difficulty retrospectively assessing ADL). We suggest that future work should prospectively collect simple geriatric parameters - e.g. basic and instrumental ADL, cognition (e.g. clock draw), and nutritional screening (mini nutritional assessment [MNA] or albumin/GNRI) before therapy. Such a comprehensive geriatric assessment (CGA) can reveal vulnerabilities missed by ECOG/CIRS alone. Indeed, even among older lymphoma patients with good ECOG, 25% to 66% had at least one geriatric impairment. In the Spanish geriatric-hematology study, routine CGA by geriatricians stratified lymphoma patients into frailty categories with dramatically different 2-year OS and treatment outcomes.[6] We agree with these and other authors that formal GA should be incorporated in prognostic modeling, as it "permits patient classification by level of frailty" that correlates with survival. At minimum, Lia *et al*. might consider using

surrogate scales for functionality (e.g. Katz ADL, Lawton IADL, or the G8 screening tool) in future analyses or validations. Failing to include these domains risks missing key aspects of frailty (nutrition, cognition, function) that could meaningfully influence outcomes.

Lastly, the derivation and application of the frailty score raise methodological concerns. Lia *et al*. assign one point to each of three variables: age at least 70 years, ECOG at least 2, and CIRS G at least 8. The result is an index that ranges from zero to three. The design is simple, but the cut points and equal weighting need stronger justification. Age 70 years may not be the optimal threshold because risk can rise sharply after 80 years, yet that nuance is lost. ECOG is treated as a binary variable, though an ECOG of 3 or 4 likely carries more risk than an ECOG of 2. A prior frailty model in older diffuse large B-cell lymphoma used weighted point values that reflected hazard ratios, and dependence in activities of daily living received greater weight than other factors.[4] Assigning equal points here implies that patients aged 70 to 79 years and those aged 80 years or more are equivalent, which may misclassify the oldest patients. We suggest testing alternative age cut points, for example separate categories for 70 to 79 and 80 or more years. We also recommend deriving weighted scores from multivariable Cox models rather than applying arbitrary thresholds. The authors state that their cut points were chosen based on distribution and predictive value, but they do not describe the process. Future work could use penalized regression or recursive partitioning to refine thresholds and weights. The study does not report the discriminative performance of the score, such as the c index, and this metric should be calculated and compared with other models. A more granular and statistically grounded approach would improve the accuracy of frailty assessment beyond the current one point per item method.

In summary, the simplified frailty index proposed by Lia *et al*. is a valuable step toward geriatric informed care in cHL, but its current form may be oversimplified. Restrictive inclusion criteria, omission of functional and nutritional domains, and unweighted scoring limit its scope and precision. We advocate for prospective validation in unselected elderly cohorts with systematic CGA, analytic refinement using modern statistical techniques, and outcome reporting that distinguishes lymphoma specific from other causes of death. Such enhancements will ensure that frailty assessment truly guides treatment decisions and improves outcomes for the most vulnerable patients with HL.

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https://doi.org/10.3324/haematol.2025.288186

Received: May 5, 2025.
Accepted: May 23, 2025.
Early view: June 5, 2025.

Disclosures

No conflicts of interest to disclose.

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