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RESEARCH LETTER

A proposed refined definition of acute myeloid leukaemia patients ineligible for intensive therapy: The Integrated Comorbidity–ECOG–Age criteria

To the Editor,

Acute myeloid leukaemia (AML) is a rare, aggressive haematological malignancy that primarily affects older adults, with a median age at diagnosis of around 70 years in so-called Western countries.[1] Although some subsets of patients, especially at a younger age, respond well to current treatment options, the overall prognosis to date remains poor. Current treatment decisions depend on both molecular disease characteristics and patient fitness. Intensive induction chemotherapy (IC) followed by consolidation, often including allogeneic haematopoietic stem cell transplantation, is the established curative approach but requires adequate physiological reserve.[2–4] Patients considered physiologically unfit are typically treated with less-intensive systemic therapies or best supportive care. Historically, options for these patients were limited, but recent approvals of venetoclax, glasdegib and ivosidenib (for Isocitrate-dehydrogenase-1 [IDH1]-mutated AML) have expanded therapeutic possibilities[2–4] making accurate fitness assessment increasingly critical. However, current guidelines lack a universally accepted framework, and existing criteria such as the Ferrara criteria[5] have been challenged for rigidity, particularly the reliance on chronological age, especially by Health Technology Assessment bodies. The European LeukemiaNet (ELN) has emphasized the need for more individualized approaches to guide treatment selection.[3,4,6]

To address this gap, this work sought to derive a refined definition for AML patients ineligible for IC, based on parameters identified in the literature and guidelines. This work aims to evaluate physiological patient fitness rather than molecular and disease-related risk factors that could limit the benefit of IC. Patients described as ineligible or 'unfit' for IC are expected to have an increased likelihood for adverse effects of IC, reduced capacity to recover from IC-induced tissue damage and reduced avidity of their immune system, questioning the safety and benefit–risk ratio of IC. Our methodology involved an exploratory literature review focusing on treatment guidelines, disease indices, clinical trials and other scientific publications focusing on patient fitness for intensive AML therapy. Together with expert medical and scientific opinion, we developed the Integrated Comorbidity–ECOG–Age (ICEA) criteria using easily applicable thresholds and rational combinations of standard clinical parameters.

We identified 21 relevant sources, including guidelines, disease indices, reviews and peer-reviewed publications discussing patient eligibility for IC. Furthermore, we identified three large registrational clinical trials designed to include AML patients ineligible for IC: VIALE-A,[7] BRIGHT AML 1003[8] and AGILE.[9,10] Most of these sources consider Eastern Cooperative Oncology Group performance status (ECOG-PS), physiological functioning (comorbidities) and, to varying degrees, age, largely aligning with the considerations that historically informed physician-driven enrolment into non-intensive treatment arms in landmark UK trials like AML16 and LI-1.[11] A systematic review indicated that age, PS and comorbidities predict the long-term and short-term mortality in older adults (≥55 years).[12] Current guidelines emphasize individual assessment and physician experience, recommending evaluation at experienced treatment centres.[2–4,13–15] However, consensus on specific physiologic thresholds is lacking.[2–4] Table S1 provides an overview of the criteria extracted from this literature search.

Age, PS and comorbidities are key determinants of eligibility for IC in AML. Most guidelines, including European Society For Medical Oncology (ESMO), National Comprehensive Cancer Network (NCCN) and ELN,[2–4,13] recognize age ≥75 years as a critical threshold due to high toxicity and poor long-term outcomes, while age ≥60 years is associated with worse prognosis, unfavourable cytogenetics and reduced treatment benefit. Studies confirm markedly lower survival in older patients. ECOG-PS strongly influences treatment decisions; patients with ECOG-PS 0–1 generally tolerate IC better, whereas ECOG-PS ≥2 correlates with higher early mortality and toxicity, especially when combined with advanced age. Comorbidities further complicate fitness assessment, with indices such as Charlson Comorbidity Index (CCI), Hematopoietic Cell Transplantation-specific-Comorbidity Index (HCT-CI) and Acute Myeloid Leukemia-Composite Model (AML-CM) used to quantify risk. Severe organ dysfunction (cardiac, renal, hepatic, pulmonary) or psychiatric disease is widely cited as a reason to avoid IC. The European LeukemiaNet

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expert panel recommendations for fitness assessment in AML emphasizes an integrated approach, considering age, ECOG-PS and comorbidity burden rather than relying on single parameters as well.[6]

Based on these findings, we derived the ICEA criteria. This approach considers age with thresholds of ≥75 and ≥60 years: (I) age ≥75 years and ≥1 comorbidity (of any organ class) or (II) age ≥60 years and contraindications for cytarabine/daunorubicin or (III) age ≥60–<75 years and (a) ECOG-PS ≥3 or (b) ECOG-PS = 2 and ≥2 relevant comorbidities* or (c) ECOG-PS ≤1 and ≥3 relevant comorbidities* (* of critical organ classes) (Figure S1).

Unlike more rigid frameworks such as the Ferrara criteria,[5] an integrated approach enables a more individualized assessment of 'fitness' for IC in AML. Relying on a single cut-off—whether chronological age or a specific organ threshold—often fails to capture the clinical interplay that determines tolerance, toxicity risk and meaningful benefit.[3,4,6] In practice, comorbidity burden is heterogeneous and extends beyond cardiac, pulmonary, renal and hepatic dysfunction; psychiatric disease, cognitive impairment and cumulative multiorgan compromise can substantially affect treatment risk. Fitness is therefore best conceptualized along a continuum where combinations of parameters—rather than isolated thresholds—inform whether IC is appropriate or less intensive strategies are preferable.

In the past, authorities have questioned oversimplified fitness definitions, for example, age ≥75 years by itself as insufficient to deem a patient ineligible for IC, or ECOG-PS 2 without relevant comorbidities. This stance reflects the need for clinical decisions that are both evidence-based and transparently justified beyond trial inclusion criteria. A structured, flexible framework addresses this need by allowing clinicians to document why certain combinations—such as moderate PS impairment with multiple noncritical comorbidities or advanced age with preserved PS but high cumulative organ burden—shift the balance towards non-intensive therapy. Such an approach encourages harmonization between real-world practice and trial interpretation. Importantly, patient-reported physical and social functioning and baseline quality of life can add nuance to fitness judgements, but their routine collection is uncommon in trials; therefore, these dimensions should complement core clinical parameters when they are available and reliable.

A flexible construct offers several advantages for front-line decision-making: it broadens comorbidity representation beyond a narrow set of 'critical' organs; and it codifies clinical reasoning without forcing restrictive cut-offs that may miss context. At the same time, any framework must remain pragmatic: it should be implementable at the bedside, rely on information routinely collected in oncology practice and be transparent. Operationalization can be aided by standardized checklists that capture age, ECOG-PS, cumulative comorbidity indices (e.g. CCI, HCT-CI, AML-CM) and modifiers such as frailty markers or polypharmacy. Regular reassessment is essential, recognizing that 'fitness' is not static; PS and organ function can change with disease control and decisions should adapt accordingly.

Notwithstanding, several limitations must be acknowledged. First, the ICEA criteria represent a proposal based on current literature and clinical expertise. Validation in future clinical studies, ideally prospective and multicentre, is necessary to test predictive performance and reproducibility across clinicians. In this context, further work could be considered to assess a dynamic, longitudinal application during treatment and the potential feasibility of a scoring system. Second, documentation, variability and quality may affect classification, particularly for comorbidities outside the traditional cardiac, pulmonary, renal, hepatic domains; standard definitions and training will be necessary to reduce inconsistency. Third, frailty—distinct from comorbidity—remains underrepresented in many datasets despite its recognized prognostic relevance. Comprehensive geriatric assessment tools, such as the Timed Up-and-Go and activities of daily living measures, are recommended in older adults and should be integrated prospectively, yet they were not routinely collected in prior approval trials, limiting immediate incorporation. Fourth, while a flexible framework improves clinical fidelity, it must avoid becoming overly complex; feasibility depends on balancing granularity with usability and on embedding assessments into workflows without delaying care. Finally, any classification system should complement—rather than substitute—clinical judgement and shared decision-making, accounting for patient preferences, goals of care and ethical considerations around risk tolerance and expected benefit. Importantly, poor outcomes observed with predominantly non-intensive treatment strategies should not be interpreted as evidence that IC is universally contraindicated in these patients. For instance, survival differences across age groups largely reflect selection effects, and a subset of carefully selected older patients can derive meaningful benefit from IC.

In summary, a tailored, combination-based approach to defining ineligibility to IC options in AML can better align at the first step of treatment selection with patient heterogeneity and contemporary therapeutic choices and provided that it is prospectively validated, standardized for consistent use and augmented by geriatric assessment where appropriate.

KEYWORDS

AML, fitness assessment, less-intensive treatment

AUTHOR CONTRIBUTIONS

Bettina Barthel: Conceptualization; investigation; methodology. **Doris Glaser:** Conceptualization; investigation; methodology. **Michael Heuser:** Conceptualization; methodology; writing – review and editing. **Daniel Weidl:** Conceptualization; methodology; investigation; writing – original draft; writing – review and editing. **Lars Bullinger:** Conceptualization; writing – review and editing. **Myrto Boukovala:** Conceptualization; writing – review and editing; writing – original draft.

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CONFLICT OF INTEREST STATEMENT

DW, MB, DG and BB are employees of Servier. LB received honoraria from AbbVie, Amgen, Astellas, Bristol Myers Squibb, Celgene, Daiichi Sankyo, Gilead, Hexal, Janssen, Jazz Pharmaceuticals, Menarini, Novartis, Otsuka, Pfizer, Roche, Sanofi and Servier and research funding from Bayer, Jazz Pharmaceuticals. MH received research funding to institution from Abbvie, Bayer Pharma AG, Jazz Pharmaceuticals, Glycostem, Karyopharm, PinotBio, Servier, Toray and honoraria from Astellas, Daiichi Sankyo, Janssen, Miltenyi, Otsuka, Qiagen, Servier and did consultancy for Abbvie, AvenCell, Ascentage Pharma, Bristol Myers Squibb, Janssen, Jazz Pharmaceuticals, LabDelbert, Novartis, Pfizer, Servier.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

AI DISCLOSURE

Artificial intelligence (AI)-based tools were used to assist with English language editing, language optimization and text summarization. All content was critically reviewed and approved by the authors.

Daniel Weidl[1]
Myrto Boukovala[1]
Doris Glaser[1]
Bettina Barthel[1]
Lars Bullinger[2,3,4]
Michael Heuser[5]

[1]*Servier Deutschland GmbH, Munich, Germany*
[2]*Department of Hematology, Oncology and Cancer Immunology, Charité—Universitätsmedizin Berlin, Berlin, Germany*
[3]*German Cancer Consortium (Deutsches Konsortium Für Translationale Krebsforschung, DKTK), Partner Site, Berlin, Germany*
[4]*National Center for Tumor Diseases (NCT), Partner Site, Berlin, Germany*
[5]*Department of Internal Medicine IV, University Hospital Halle (Saale), Martin-Luther-University Halle-Wittenberg, Halle, Germany*

Correspondence
Daniel Weidl, Servier Deutschland GmbH, Munich, Germany.
Email: daniel.weidl@servier.com

ORCID

Daniel Weidl https://orcid.org/0009-0008-3137-575X
Lars Bullinger https://orcid.org/0000-0002-5890-5510
Michael Heuser https://orcid.org/0000-0001-5318-9044

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