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REVIEW

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Assessing eligibility for treatment in acute myeloid leukemia in 2023

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ABSTRACT

Introduction: Age has historically been considered the main criterion to determine eligibility for intensive chemotherapy in patients with acute myeloid leukemia (AML), but age alone can no longer be considered an absolute indicator in determining which patients should be defined as unfit. Assessment of fitness for a given treatment today serves an important role in tailoring therapeutic options.

Areas covered: This review examines the main options used in real life to define eligibility for intensive and nonintensive chemotherapy in patients with AML, with a main focus on the Italian SIE/SIES/GITMO Consensus Criteria. Other published real-life experiences are also reviewed, analyzing the correlation between these criteria and short-term mortality, and thus expected outcomes.

Expert opinion: Assessment of fitness is mandatory at diagnosis to tailor treatment to the greatest degree possible, evaluating the patient's individual profile. This is especially relevant when considering the availability of newer, less toxic therapeutic regimens, which have shown promising results in patients with AML who are older or considered unfit for intensive treatment. Fitness assessment is now a fundamental part of AML management and a critical step that can potentially influence outcomes and not just predict them.

PLAIN LANGUAGE SUMMARY

In patients with acute myeloid leukemia (AML), age has generally been considered as the main factor to determine if intensive chemotherapy can be carried out (fitness). However, this has been gradually changing in recent years. In addition to age, comorbidities and overall performance status are also important in determining if the patient should undergo intensive chemotherapy and have an important role in tailoring therapeutic options. Consensus criteria to define eligibility for intensive and nonintensive chemotherapy in patients with AML have been proposed, which have been shown to correlate well with expected outcomes. Today, given the evolution of the treatment armamentarium, assessment of a patient's 'fitness' is compulsory to select the most appropriate treatment for each patient.

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KEYWORDS
Acute myeloid leukemia; intensive chemotherapy; fitness; elderly; comorbidities; Italy; performance status; geriatric scores

1. Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematologic malignancy and, although rare, is the most common acute leukemia subtype and has the poorest prognosis [1]. The prevalence of AML varies greatly among different geographic regions worldwide, with a burden for healthcare systems that has been steadily increasing in recent years [1,2]. The risk of AML is highly dependent on age, with a prevalence that increases substantially after 55 years of age [1–3]. AML is thus more common in older versus younger individuals, with significant differences in terms of outcome [2,4]. The 5-year overall survival (OS) of patients with AML is <25% and <10% in patients 60 to 65 and ≥70 years old, respectively, compared with 50% for those <50 years [1,5]. Between 2000 and 2010, only 40% of patients ≥65 years received AML-directed therapy. This treatment disparity was more pronounced in the oldest group of patients (>80 years); in this group, only 20% received anti-leukemic treatment. This is not surprising considering that, until recently, treatment strategies included mainly chemotherapy, fewer less-intensive therapies (hypomethylating agents [HMAs]), and best supportive care [6], with few options to affect OS in those patients who are not considered eligible for intensive chemotherapy. From a clinical management standpoint, the first step in assessing treatment for elderly patients has generally been to evaluate their fitness in terms of ability to tolerate intensive induction chemotherapy.

In recent years, less intensive, non-chemotherapy frontline options have expanded greatly (Table 1) and are leading to a paradigm shift for the treatment of older patients with AML and to a renewed interest in the assessment of fitness in these patients in order to choose the best option (3). Following a brief overview of available treatment options for AML, the objective of the present review is to summarize current knowledge regarding the concept of

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Article highlights

- Age has historically been considered the main criterion to determine eligibility for intensive chemotherapy in patients with acute myeloid leukemia (AML).
- Assessment of comorbidities and performance status is now essential in defining overall fitness for a given treatment.
- Among multiparameter tools, the Italian SIE/SIES/GITMO Consensus Criteria defines eligibility for intensive chemotherapy in patients with AML and shows good correlation with expected outcomes.
- In light of recent advances in the therapeutic armamentarium for AML, for patients who are not eligible for intensive chemotherapy comprehensive fitness assessment is now a fundamental part of their management to ensure that the best therapeutic option can be offered.

fitness assessment and the criteria used to measure it while considering the recent advances in treatment.

2. Treatment options in AML

The choice of frontline treatment in AML is increasing in complexity and is even more challenging in patients >60 years [9]. In addition to fitness, age, and clinical parameters, the choice of treatment also depends on the cytogenetic and molecular profile of the disease [9–11].

Treatment options for AML have been historically divided into intensive and non-intensive regimens (Table 1). Traditionally, standard intensive induction therapy is 7 days of cytarabine and 3 days of an anthracycline (7 + 3 regimens). Several studies highlighted that, given their unfavorable cytogenetics and poor performance status, older patients have a high likelihood of post-induction early death, with low chances of benefit [12,13]. This gave rise to the possibility of using less toxic therapeutic regimens in older patients, including HMAs [14,15]. Since the early 2000s, HMAs have been providing significant benefit to older patients with AML. They were the first alternative to supportive care for unfit patients and remained the only option available to them for years, even though they did not provide long-term results, and partially satisfying the unmet medical need for this subset of patients [16,17].

Table 1. Available care regimens and drugs for patients with AML [7–9,19].

Therapy	Regimen
Intensive chemotherapy	• 7 + 3 regimen • Midostaurin • Gemtuzumab ozogamicin • Gilteritinib • Liposomal daunorubicin + cytarabine
Non-intensive therapy	• Azacytidine • Decitabine • Low-dose cytarabine • Venetoclax + HMA • Glasdegib • Ivosidenib ± HMA • Enasidenib
Best supportive care	• Hydroxyurea • Low-dose cytarabine • Palliative care

7 + 3 regimen, 7 days of cytarabine and 3 days of an anthracycline; AML, acute myeloid leukemia; HMA, hypomethylating agent.

Several new therapies have been approved for use in AML in recent years, which has further expanded the number of therapeutic options [18]. In patients who are not considered candidates for intensive chemotherapy, new treatment options are now available or in development, which include B-cell lymphoma 2 (BCL-2) inhibitors, FMS-like tyrosine kinase 3 (FLT3) inhibitors, Smoothened Inhibitors (SMO), and Isocitrate dehydrogenase 1 and 2 (IDH1/2) inhibitors [9–11,19]; as a consequence, the use of best supportive care remains limited to the most unfit patients or those not willing to undergo therapy.

The BCL-2 inhibitor venetoclax has been tested and approved in combination with different induction regimens in AML patients ineligible for intensive chemotherapy. Venetoclax with decitabine or azacitidine was effective and well tolerated in older patients with AML in a Phase1b study, following which FDA granted accelerated approval for the novel combination [20]. Venetoclax and azacitidine vs. placebo and azacitidine were further evaluated in the VIALE-A Phase 3 study [21]. Median OS was 14.7 months in the azacitidine-venetoclax group and 9.6 months in the control group (HR for death, 0.66; 95% CI, 0.52 to 0.85; P < 0.001). Given the results of these two studies, the EMA granted approval for the combination of venetoclax and azacitidine.

Together with low-dose cytarabine, venetoclax has been shown to provide clinically-meaningful remission rates and OS compared to low-dose cytarabine in patients with AML who are unfit for intensive chemotherapy in the Phase 3 VIALE-C trial [22]: median OS was 7.2 vs 4.1 months, respectively (HR, 0.75; 95% CI, 0.52–1.07; P = 0.11). This combination has been approved by the FDA.

In IDH1-mutated newly diagnosed AML patients ineligible for intensive chemotherapy, ivosidenib and azacitidine showed significant clinical benefit in the Phase 3 trial AGILE as compared with placebo and azacytidine [23]. Median OS was 24.0 months with ivosidenib and azacitidine vs. 7.9 months with placebo and azacitidine (HR for death, 0.44; 95% CI, 0.27 to 0.73; P = 0.001). Recently, according to the Phase 3 AGILE study results, the CHMP (Committee for Medicinal Products Human Use) has issued a Positive Opinion on the combination of ivosidenib with azacitidine in this setting of patients. This combination regimens is approved by the FDA ,while evaluation by the EMA is still in progress.

Glasdegib and LDAC vs. LDAC demonstrated superior OS in patients with AML ineligible for intensive chemotherapy (median OS was 8.3 versus 4.3 months, HR 0.495; (95% CI 0.325–0.752) in the Phase II BRIGHT AML 1003 trial [24]. The clinical benefit was particularly prominent in patients with secondary AML. Glasdegib + LDAC is approved by FDA and EMA for the aforementioned indication [25,26].

In a recent Phase 3 trial named LACEWING in patients with AML ineligible for intensive chemotherapy and *FLT3* mutation, the combination of gilteritinib and azacitidine was associated with significantly higher composite complete remission rates than azacytidine alone (4.53 months vs. 0.03 months) but with similar OS compared to azacytidine monotherapy [23].

Gilteritinib resulted in significantly longer survival and higher percentages of patients with remission than salvage chemotherapy among patients with relapsed or refractory FLT3-mutated AML in Phase 3 ADMIRAL trial that enrolled patients refractory to one or two cycles of conventional anthracycline-containing induction therapy or if they had hematologic relapse after a complete remission (median age = 62.0 years) [27]. Gilteritinib is approved by FDA and EMA as monotherapy for the treatment of adult patients who have relapsed or refractory AML with a FLT3 mutation.

IDH inhibitors in combination with HDAC inhibitors also seem to be promising in unfit patients [28,29]. Lastly, CAR-T therapy is also making rapid progress, and many potential targets have been identified, although its use in older and unfit patients requires further study [30].

At present, it is also important to highlight that treatment is becoming increasingly personalized given the discovery of new molecular drivers of disease and progression [31,32].

Therefore, the expansion of the therapeutic armamentarium and the opportunity to restrict the use of best supportive care to a few, very select situations, such as patients considered frail and not candidate to currently available non-intensive therapies, has revitalized interest in the definition of treatment eligibility and its importance in daily clinical practice.

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) give detailed treatment recommendations based on patient characteristics, such as age, presence of comorbid conditions affecting performance status, and preexisting myelodysplasia [11]. Among the recommendations is that patients with poor performance status, significant comorbidities, and/or advanced age (i.e. some patients ≥60 years old and most patients ≥70 years old) should receive low-intensity therapy or supportive care if a clinical trial is not available [11]. The European LeukemiaNet (ELN) guidelines also state that age alone should not be the major determinant for choice of therapy and that older, medically fit patients are likely to benefit more from intensive versus non-intensive therapy [10]. Poor performance status and comorbidities should also be taken into consideration.

Canadian guidelines developed specifically for older patients with AML recommend that intensive induction therapy should be considered for all patients <80 years, except those with high comorbidity scores and those with adverse risk cytogenetics who are not potential candidates for hematopoietic stem cell transplantation (HCT) in complete remission [33]. However, the guidelines specify that there is no consensus as to what degree of comorbidity constitutes an absolute contraindication. It is further specified that, although comorbidity indices are valuable geriatric assessment tools that can assess physical function and cognition and provide important information regarding suitability for intensive chemotherapy, such tools should not replace clinical judgment.

The 2020 European Society for Medical Oncology guidelines for AML [34] state that the initial assessment of patients with newly diagnosed AML should focus on patient fitness for standard induction and consolidation chemotherapy. The guidelines further state that preexisting heart, kidney, lung, or liver disease; mental illness; an Eastern Cooperative Oncology Group (ECOG) performance score ≥3; and age ≥75 years are the strongest predictors for non-relapse induction-related mortality and should be considered to determine ineligibility to intensive induction and consolidation chemotherapy. In addition, it is stated that the hematopoietic cell transplantation-specific comorbidity index (HCT-CI) score can predict treatment-related mortality in patients treated with induction chemotherapy, as well as transplant outcome. As in other guidelines, the final decision should be made only after careful consultation between physician and patient.

Other authors have developed guidance that is specific to older patients with AML, all emphasizing the need for personalized assessment and treatment plans as an essential part of care [4,9,19,35].

3. Fitness assessment – single parameters

3.1. Age

The World Health Organization defines 65 years as the age of transition to 'elderly.' The United Nations considers the transition to take place at 60 years, taking into account the low life expectancy of those living in disadvantaged geographic areas [36]. Older age was historically considered the main criterion for determining whether a patient could receive intensive chemotherapy. The effects of age on the patient and disease-related factors are well known, resulting in a higher incidence of early death after induction chemotherapy and a lower chance for complete response and long-term survival [12,13].

AML in older adults is a clinical entity distinct from the disease in younger patients in terms of both disease- and patient-specific characteristics [12]. Older patients with AML tend to present with lower white blood cell counts and marrow blast percentage, and multidrug resistance is also almost two-fold higher in patients >75 years old compared with those <56 years old [12]. Moreover, fewer than 5% of patients with AML >75 years old have favorable cytogenetics compared with 20% in younger patients [12]. Many of these differences can be attributed to mutations in hematopoietic cells that are associated with the aging process [37]. In this view, the discovery of the link between aging, occurrence of clonal hematopoiesis of indeterminate prognosis, and propensity to develop AML represents a considerable step forward. In addition, rates of secondary AML, which is more resistant to chemotherapy, increase with age [38]. All these factors have an effect on prognosis, response to therapy, and final outcome, with older patients being disfavored [4].

However, although fitness is mostly related to age, it is clear that age alone cannot be used as an absolute indicator to determine which patients should be defined as unfit [4]. There are several instances of younger patients with comorbidities having a poorer performance status than someone older but healthier. This raises the critical question of whether biological age truly correlates with chronological age, because it has become clear that chronologic age should not be the only criteria for determination of fitness or for treatment choice [13,39].

3.2. Comorbidities

The presence of comorbidities has the potential to affect response to treatment and toxicity [19]. Assessment of comorbidities is useful to help define overall fitness for a given treatment [40,41]. Compared with less aggressive neoplasms, AML required until recently the use of intensive therapies to achieve remission of the disease, making comorbidities more relevant than other geriatric parameters in the assessment of fitness during treatment. Indeed, Etienne et al. reported that comorbidities are an independent predictor of complete remission in patients who received induction therapy for AML [42].

One of the most common tools for evaluation of comorbidities is the Hematopoietic cell transplantation (HCT) - specific comorbidity index, which includes not only objective definitions and number of comorbidities but their level of burden [43]. The HCT-CI has been shown to predict early death and survival among patients >60 years old and undergoing induction therapy for AML [44].

It is important to consider that a patient with a well-managed comorbidity could be fit for intensive therapy. Evaluation of comorbidities may aid in identifying a patient's overall fitness for intensive therapy, but it cannot predict tolerability of treatment for AML with absolute certainty because other factors must be considered as well [19,40,41].

3.3. Performance status

The interaction between age and performance status has been investigated in several studies. According to Kadia et al., age had a profound effect on outcome in patients with poor performance status and appeared to have just a modest effect on the outcome of older patients with excellent performance status [45]. Performance status can also help to identify patients who are medically unfit independent of age and is routinely evaluated using either ECOG performance score or the Karnofsky index [19]. Of note, in adults with poor performance scores, both 30-day mortality and treatment toxicity are higher [40]. Poor performance scores have also been associated with lower rates of complete response, higher 8-week mortality, and shorter OS [46,47]. Real-world data have further confirmed that, in addition to age, performance status is strongly related to survival outcomes and complete remission [13]. An analysis of 2767 patients with AML in the Swedish Acute Leukemia Registry evaluated the effect of the decision to treat on outcomes [13]. Performance status was highest in patients aged 40 to 44 years and declined with increasing age. As performance status worsened, the proportion of patients receiving intensive therapy also declined. Thirty-day mortality rates were dependent on age and performance status, but older patients with good performance status had low early death rates and patients with poor performance status had increased early mortality across all ages.

4. Fitness assessment – multi-parameter tools

4.1. Fitness scores

Given the limitations of using single parameters to define patient fitness and to guide treatment decisions, several studies have been conducted in an attempt to combine multiple variables to determine fitness.

In a single-center study of 85 consecutive patients >60 years of age with newly diagnosed AML [48], several tools were used to compare outcomes, including the local geriatric G8 screening tool (seven items from the Mini Nutritional Assessment questionnaire and age), HCT-CI comorbidity score, and AML scores proposed by the German Acute Myeloid Leukemia Cooperative Group. Median survival time for fit patients was 10 months compared with 3.4 months for unfit patients using physician evaluation. Parallel evaluation of fitness according to the proposed cut-point of the G8 tool also significantly discriminated patient survival. However, the correlation between frailty evaluated using the HCT-CI and physician evaluation was moderate, although it was concluded that frailty scores can help to improve the prediction of prognosis. Similar results were seen in another single-center study in 130 patients aged ≥60 years (median age, 71.2 years) [49]. However, the G8 score is quick and easy to apply and has good generalizability for cancer patients [50].

Frailty evaluated using the G8 tool, Sorror index, and AML score applied to older patients at AML diagnosis all seemed to help discriminate older patients with AML when considering overall survival. In 2017, Sorror and colleagues developed a composite AML model combining age, an augmented HCT-CI, and aggressiveness of AML, to predict early and late mortality. In a population of 1100 newly diagnosed patients with AML aged 20 to 89 years, the composite model correlated with 1-year mortality and seemed to be able to guide decision-making in AML [51]. This composite score may possibly identify patients who do not benefit from intensive chemotherapy [50]. A summary of fitness tools is provided in Table 2.

4.2. Geriatric assessment tools

Geriatric assessment tools aim at evaluating health status in older patients and typically include multiple domains, such as cognition, depression, functional and nutritional status, frailty, and mental health [59]. Many studies have documented that geriatric assessment can predict tolerability of chemotherapy, treatment discontinuations, therapy-related hospitalizations, and survival in the geriatric oncology population [59]. As an example, in a study by Klepin et al. in a cohort of 74 consecutive patients with AML aged >60 years, they found that poor cognitive function and low physical performance were able to predict shorter OS [60]. In another retrospective study in 195 patients aged >60 years with newly diagnosed AML or myelodysplastic syndrome, the value of geriatric and quality-of-life assessment was investigated [61]. The authors identified a Karnofsky index below 80%, European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire score for fatigue ≥50, and impairments in activities of daily living as the strongest prognostic factors, together with the well-known bone marrow blasts count and cytogenetics. Unfitness criteria for HMA therapy were also identified using these parameters. However, the score developed by Klepin et al. is generally considered to be time-consuming [50].

Table 2. Different models and scores to assess patients' fitness and eligibility for intensive chemotherapy* [50].

Score	No. of patients	Score variables	Specificities
Early mortality and survival predictive models			
Malfuson et al. (2008) [52]	416	Age, WBC, PS, cytogenetic risk	Predictive of mortality or survival, not proper fitness scores, therapy-specific, inclusive of disease features
Wheatley et al. (2009) [53]	2483	Age, WBC, PS, cytogenetic risk, type of leukemia (de novo vs. secondary)	
Kantarjian et al. (2010) [47]	446	Age, PS, cytogenetic risk, creatinine	
Krug et al. – AML Score (2010) [54]	1406	Age, body temperature, Hb, platelet count, fibrinogen, type of leukemia (de novo vs. secondary)	
Walter et al. – TRM Score (2011) [55]	3365	Age, PS, platelet count, WBC, peripheral blood blast percentage, albumin, creatinine, type of leukemia (de novo vs. secondary)	
Geriatric assessment scores			
Soubeyran et al. – G8 Score (2008) [56] Soubeyran et al. (2011) [57]	364, 1668	Seven Mini Nutritional Assessment (MNA) items (appetite, weight loss, motricity, BMI, cognition and depression, self-related health, medications), age	Quick and easy to apply, generalizability for cancer patients
Deschler et al. (2013) [61]	195	PS (Karnofsky index), activities of daily living (ADL) and QoL/fatigue	Time consuming
Klepin et al. (2013) [60]	74	Cognition, psychological function, physical function, comorbidity	
Sherman et al. (2013) [58]	101	Comorbidity, physical function, pain	
Comorbidity and organ function scores			
Sorror et al. – HCT-CI Score (2005) [43]	1055 (+ 347)	Comorbidities	Originally developed to assess eligibility for HCT
Sorror et al. – AML Composite Model (2017) [51]	733 (+ 367)	Age, augmented HCT-CI and cytogenetic/molecular risks	Inclusive of disease features, possibly able to identify patients who do not benefit from intensive chemotherapy
Ferrara et al. (2013) [66]; Borlenghi et al. (2021) [69]	699	Age, PS, comorbidities (cardiac, pulmonary, renal, hepatic, infections, mental illness, uncontrolled neoplasia)	Easily and widely applicable, not inclusive of disease features, able to predict benefit from more or less intensive treatments in different fitness groups (fit/unfit/frail patients)

Abbreviations. BMI, body mass index; Hb, hemoglobin; HCT, hematopoietic cell transplantation; PS, performance status; QoL, quality of life; WBC, white blood cells.
Adapted from Urbino I. et al. Cancers 2021, 13, 5075. https://doi.org/10.3390/cancers13205075

4.3. Tools for allogeneic hematopoietic stem cell transplantation

In daily practice, allogeneic hematopoietic stem cell transplantation (allo-HSCT) is being increasingly applied, although it is associated with considerable morbidity and mortality, especially in the elderly [50]. The HCT-CI can be used to predict non-relapse mortality in patients undergoing allo-HSCT, although it does not correlate well with outcomes in the elderly [43]. The EBMT score uses age, disease status, time passed from diagnosis to transplant, as well as the donor recipient sex combination and type to help select candidates for HSCT [62]. In 2021, a study from Japan reported that age, sex, ECOG, HCT-CI, and donor type were associated with non-relapse mortality, forming the NRM-J index [63]. The NRM-J was significantly more accurate than the EBMT score in predicting non-relapse mortality after allo-HCST and thus may potentially be of value in treatment-decision making following allo-HCST. Other authors have pointed out that frailty may be associated with adverse outcomes after allo-HCST [64]. While age itself should not be used as a criterion to determine eligibility for allo-HCST, multidimensional geriatric assessment with the Fondazione Italiana Linfomi (FIL) score has been reported to add useful prognostic information [65].

4.4. SIE/SIES/GITMO consensus criteria

In 2013, Ferrara et al. published a definition of unfitness for intensive and non-intensive chemotherapy in patients with AML that was developed using a Delphi consensus-based process involving a panel of Italian hematologists under the auspices of the Italian Society of Hematology (SIE), Italian Society of Experimental Hematology (SIES), and Italian Group for Bone Marrow Transplantation (GITMO) [66]. The process took into consideration that therapies interfering with age-related frailty, producing organ intolerance, and potentially reducing life expectancy owing to comorbidities, should be avoided. According to the 'Ferrara criteria,' unfitness to intensive chemotherapy requires the fulfillment of 1 of 9 conditions and unfitness for non-intensive chemotherapy requires at least 1 of 6 conceptual criteria (Table 3). The panel further identified 15 operational criteria to define unfitness to intensive chemotherapy and unfitness to non-intensive chemotherapy (Table 4). The consensus-based definitions thus provided definitions of unfitness for intensive and non-intensive chemotherapy in patients with AML linking for the first time the presence of a set of geriatric and comorbidity parameters to a specific treatment choice. Overall, the SIE/SIES/GITMO Consensus Criteria are easily

Table 3. Conceptual criteria used to define patients not fit for conventional intensive chemotherapy and non-intensive therapies in AML [66].

Conceptual criteria defining patients not fit for conventional intensive chemotherapy*
• Advanced age (i.e. >75 years)
• Severe cardiac comorbidity
• Severe pulmonary comorbidity
• Severe renal comorbidity
• Severe hepatic comorbidity
• Active infection resistant to anti-infective therapy
• Cognitive impairment
• Low performance status (ECOG functional scale)
• Any other comorbidity that the physician judges to be incompatible with chemotherapy
Conceptual criteria defining patients not fit for non-intensive chemotherapy
• Very severe cardiac comorbidity
• Severe pulmonary comorbidity
• Severe hepatic comorbidity
• Active infection resistant to anti-infective therapy
• Cognitive impairment
• Uncontrolled neoplasia

*Only 1 of the criteria needs to be met by the patient to be defined as not fit.
AML, acute myeloid leukemia; ECOG, Eastern Cooperative Oncology Group.

and widely applicable, and able to predict benefit from more or less intensive treatments in different fitness groups (fit/unfit/frail patients) [50].

Since its publication in 2013, the Ferrara criteria have entered clinical practice in Italy and several studies have been conducted to validate their usefulness. Overall, these studies have shown good correlation between proposed criteria and short-term mortality and, thus, expected outcomes with intensive chemotherapy (Table 5).

Table 4. Operational criteria used to define patients not fit for conventional intensive chemotherapy and non-intensive therapies in AML [66].

Operational criteria defining patients not fit for intensive chemotherapy
• Age >75 years
• Congestive heart failure or documented cardiomyopathy with an EF ≤50%
• Documented pulmonary disease with DLCO ≤65% or FEV1 ≤ 65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
• On dialysis and age >60 years or uncontrolled renal carcinoma
• Liver cirrhosis Child B or C, or documented liver disease with marked elevation of transaminases (>3 times normal values) and age >60 years, or any biliary tree carcinoma or uncontrolled liver carcinoma or acute viral hepatitis
• Active infection resistant to anti-infective therapy
• Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
• ECOG performance status ≥3 not related to leukemia
• Any other comorbidity that the physician judges to be incompatible with conventional intensive chemotherapy
Operational criteria defining patients not fit for non-intensive chemotherapy
• Refractory congestive heart failure
• Documented pulmonary disease with DLCO ≤65% or FEV1 ≤ 65%, or dyspnea at rest or requiring oxygen, or any pleural neoplasm or uncontrolled lung neoplasm
• Liver cirrhosis Child B or C or acute viral hepatitis
• Active infection resistant to anti-infective therapy
• Current mental illness requiring psychiatric hospitalization, institutionalization, or intensive outpatient management, or current cognitive status that produces dependence (as confirmed by the specialist) not controlled by the caregiver
• Uncontrolled neoplasia

AML, acute myeloid leukemia; DLCO, diffusing capacity of the lungs for carbon monoxide; ECOG, Eastern Cooperative Oncology Group; EF, ejection fraction; FEV1, forced expiratory volume in 1 second.

In a retrospective analysis by Palmieri et al., the Ferrara criteria were applied to 180 consecutive patients with AML (125 patients >60 years old; 55 patients <60 years old; median age, 66 years) treated in a single-institution setting [67]. Interestingly, the risk stratification did not differ between the two groups of patients (younger vs older), confirming that risk distribution cannot be simply an age-related factor. A high degree of concordance was observed between these 'operational criteria' and outcomes, with an overall survival of 15.3 months, 8.6 months, and 1 month for fit, unfit, and frail patients, respectively.

In 2020, Palmieri et al. used the Ferrara criteria to retrospectively evaluate the fitness of 655 adults who underwent intensive chemotherapy for AML in a US institution [68] to determine the accuracy of this assessment in predicting early mortality and survival. In their experience, the criteria had from good to very good accuracy in predicting 28-day and 100-day mortality, superior to that observed with the treatment-related mortality score, and further improved with other factors, such as albumin or performance status. Also, in this evaluation, the authors concluded that the Ferrara criteria, together with molecular/genetic data, may serve as a basis for informed decision-making in patients with AML, particularly those with older age and with comorbidities [68].

In a paper by Borlenghi et al., the criteria were retrospectively applied to a large population of 699 consecutive patients with AML, treated in 8 hematologic institutions, to validate their usefulness in the clinical setting [69]. The criteria were easily applicable to 98% of patients, and fitness independently predicted survival, as confirmed by multivariate analysis. The authors concluded that these easy-to-apply criteria, combined with biological risk evaluation, could represent a valid tool to tailor the intensity of available treatments for different patients with AML.

Borlenghi and colleagues also investigated the integration of ELN risk categories and Ferrara criteria to identify potential subgroups with different prognoses and guide treatment decision in patients with secondary AML because they represent a heterogeneous group of patients. In a retrospective analysis of 280 consecutive patients with secondary AML aged >64 years and diagnosed from 2008 to 2015, median OS survival was 10.1 months in fit patients versus 4.2 and 1.8 in unfit and frail patients, respectively [70]. Fitness evaluation was therefore shown to predict the outcomes of patients, and the authors concluded that, in addition to age, fitness evaluation should be mandatory in older patients with AML.

5. Conclusions

As overviewed herein, for comprehensive assessment of fitness a number of parameters should be assessed in addition to age, including comorbidities and performance status. To help clinicians, several fitness and assessment tools can be used. The SIE/SIES/GITMO Consensus Criteria appear to be of substantial value when personalizing therapy, and a number of studies have shown that they can accurately predict expected outcomes, and thus stratify patients by level of fitness. Moreover, these consensus criteria are easy to apply in routine practice. More widespread use of them could help

Table 5. Studies evaluating SIE/SIES/GITMO fitness criteria for treatment of older patients with AML.

					mOS, months		
Reference	Study type	Study dates	Patients, n	Age, years	Fit	Unfit	Frail
Borlenghi et al. 2018 [70]	Retro	2008–2015	280 sAML	>64	10.1	4.2	1.8
Borlenghi et al. 2021 [69]	Retro	n.r.	699 AML	Median, 74	10.9	4.2	1.8
Palmieri et al. 2019 [67]	Retro	2013–2018	180 AML	Median, 66	15.3	8.6	1
Palmieri et al. 2020 [68]	Retro	2006–2020	655 AML IC-treated	Median, 60.5	36.8	4.8	n.r.

AML, acute myeloid leukemia; IC, intensive chemotherapy; mOS, median overall survival; n.r., not reported; retro, retrospective; sAML, secondary acute myeloid leukemia.

not only to harmonize therapy in daily practice but also to reduce the variability in criteria used in clinical trials.

6. Expert opinion

Following decades of humble improvement in management of AML, new treatment options and treatment regimens are now available that may potentially improve outcomes. Assessment of fitness should thus be mandatory at diagnosis in order to tailor treatment as much as possible, taking into consideration the patient's individual profile and desires so that the best therapeutic option can be offered. This is especially relevant when considering new, less toxic therapeutic regimens, which have shown promising results in older or unfit patients with AML [45]. In addition to patient-related factors, traditional prognostic factors, such as percentage of blasts and cytogenetic and molecular aberrations, should also be taken in consideration [19]. The Ferrara criteria have been demonstrated to facilitate the choice of the most appropriate treatment regimen in older patients with AML. This easy-to-apply tool is thus of significant benefit not only in daily practice but also in clinical trials, where it may allow for greater harmonization of fitness definition. However, it should be pointed out that these criteria have not been validated in a prospective study and only retrospective analyses are available. There is thus an urgent need for prospective data that would provide additional confirmation of the utility of these criteria in routine practice. Moreover, the Ferrara criteria do not include disease features, and direct comparisons versus other scores are lacking.

To further illustrate the complexity of proper evaluation of fitness, it should be noted that, despite being related to both age and comorbidities, performance status in itself cannot be considered an accurate predictor of overall fitness for therapy, although it serves an important role in tailoring therapeutic options [40,41]. The performance status of patients with AML may consistently improve after adequate supportive measures, and it is therefore important to discriminate poor AML-dependent performance status.

Geriatric assessment can help identify impairments that may go otherwise undetected in routine evaluation [59] but, unfortunately, at present, there is no consensus on which geriatric assessment should be used or in which patients. Moreover, their applicability in daily clinical practice seems to be difficult. However, the field is moving rapidly, and very recent contributions have revitalized this area of study [71]. In this regard, the field has been moved forward by identifying reproducible tools to characterize fitness for intensive therapy that can be used in clinical trials and at the bedside to guide treatment decisions [72].

To further complicate the therapeutic decision, patients with comorbidities are often excluded from clinical trials, which limits the possibility to make evidence-based treatment decisions. The availability of newer and better-tolerated therapies has led some authors to propose that the simplistic view of fit and unfit may not be applied in all clinical situations [73]. In this regard, it has been noted that, although the Ferrara et al. consensus criteria can be useful for determining unfitness for intensive induction chemotherapy, functional and genomic biomarkers not included in the criteria are being increasingly used to guide treatment choice, given the growing number of effective therapeutic options [74]. Currently, fitness assessment seems to be fundamental part of AML management, aimed at the selection of the best therapeutic option while keeping in mind the need to achieve a balance between efficacy of therapy, treatment toxicity, and quality of life [75,76]. Thus, assessment of fitness should be viewed as a critical step that can potentially influence outcomes and not just predict them [77].

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Declaration of Interest

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Shallis RM, Wang R, Davidoff A, et al. Epidemiology of acute myeloid leukemia: recent progress and enduring challenges. Blood Rev. 2019;36:70–87.
2. Yi M, Li A, Zhou L, et al. The global burden and attributable risk factor analysis of acute myeloid leukemia in 195 countries and territories from 1990 to 2017: estimates based on the global burden of disease study 2017. J Hematol Oncol. 2020;13:72.
3. Group AW, Busco S, Buzzoni C, et al. Italian cancer figures–Report 2015: the burden of rare cancers in Italy. Epidemiol Prev. 2016;40:1–120.

4. Webster JA, Pratz KW. Acute myeloid leukemia in the elderly: therapeutic options and choice. Leuk Lymphoma. 2018;59:274–287.
5. SEER cancer stat facts: acute myeloid leukemia [Internet]. Bethesda (MD): National Cancer Institute; 2017. [cited 2022 Nov 29]. Available from: http://seer.cancer.gov/statfacts/html/amyl.html.
6. Kantarjian HM, Short NJ, Fathi AT, et al. Acute myeloid leukemia: historical perspective and progress in research and therapy over 5 decades. Clin Lymphoma Myeloma Leuk. 2021;21:580–597.
7. Dohner H, Estey E, Grimwade D, et al. Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. Blood. 2017;129:424–447.
8. Tallman MS, Wang ES, Altman JK, et al. Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw. 2019;17:721–749
9. Abdallah M, Xie Z, Ready A, et al. Management of Acute Myeloid Leukemia (AML) in older patients. Curr Oncol Rep. 2020;22:103.
10. Dohner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. Blood. 2022;140:1345–1377.
11. Pollyea DA, Bixby D, Perl A, et al. NCCN guidelines insights: acute myeloid leukemia, version 2.2021. J Natl Compr Canc Netw. 2021;19:16–27.
•• **Current US recommendations for diagnosis and treatment of AML.**
12. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. Blood. 2006;107:3481–3485.
13. Juliusson G, Antunovic P, Derolf A, et al. Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. Blood. 2009;113:4179–4187.
14. Lazarevic VL, Bredberg A, Lorenz F, et al. Acute myeloid leukemia in very old patients. Haematologica. 2018;103:e578–e580.
15. Juliusson G, Hoglund M, Lehmann S. Hypo, hyper, or combo: new paradigm for treatment of acute myeloid leukemia in older people. Haematologica. 2020;105:249–251.
16. Fenaux P, Mufti GJ, Hellstrom-Lindberg E, et al. Azacitidine prolongs overall survival compared with conventional care regimens in elderly patients with low bone marrow blast count acute myeloid leukemia. J Clin Oncol. 2010;28:562–569.
17. Kantarjian HM, Thomas XG, Dmoszynska A, et al. Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2012;30:2670–2677.
• **Pivotal trial in AML.**
18. Lai C, Doucette K, Norsworthy K. Recent drug approvals for acute myeloid leukemia. J Hematol Oncol. 2019;12:100.
19. Cortes JE, Mehta P. Determination of fitness and therapeutic options in older patients with acute myeloid leukemia. Am J Hematol. 2021;96:493–507.
20. Pollyea DA, Pratz K, Letai A, et al. Venetoclax with azacitidine or decitabine in patients with newly diagnosed acute myeloid leukemia: long term follow-up from a phase 1b study. Am J Hematol. 2021;96:208–217.
21. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383:617–629.
22. Wei AH, Montesinos P, Ivanov V, et al. Venetoclax plus LDAC for newly diagnosed AML ineligible for intensive chemotherapy: a phase 3 randomized placebo-controlled trial. Blood. 2020;135:2137–2145.
23. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. N Engl J Med. 2022;386:1519–1531.
24. Heuser M, Smith BD, Fiedler W, et al. Clinical benefit of glasdegib plus low-dose cytarabine in patients with de novo and secondary acute myeloid leukemia: long-term analysis of a phase II randomized trial. Ann Hematol. 2021;100:1181–1194.
25. FDA. [cited 2022 Nov 29]. Available at: https://www.fda.gov/drugs/fda-approves-glasdegib-aml-adults-age-75-or-older-or-who-have-comorbidities
26. EMA. [cited 2022 Nov 29]. Available at: https://www.ema.europa.eu/en/documents/product-information/daurismo-epar-product-information_it.pdf
27. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381:1728–1740.
28. Chaturvedi A, Gupta C, Gabdoulline R, et al. Synergistic activity of IDH1 inhibitor BAY1436032 with azacitidine in IDH1 mutant acute myeloid leukemia. Haematologica. 2021;106:565–573.
29. DiNardo CD, Stein AS, Stein EM, et al. Mutant isocitrate dehydrogenase 1 inhibitor ivosidenib in combination with azacitidine for newly diagnosed acute myeloid leukemia. J Clin Oncol. 2021;39:57–65.
30. Marofi F, Rahman HS, Zmj A-O, et al. Novel CAR T therapy is a ray of hope in the treatment of seriously ill AML patients. Stem Cell Res Ther. 2021;12:465.
31. Andreozzi F, Massaro F, Wittnebel S, et al. New perspectives in treating acute myeloid leukemia: driving towards a patient-tailored strategy. Int J Mol Sci. 2022;23(7):3887.
32. Newell LF, Cook RJ. Advances in acute myeloid leukemia. BMJ. 2021;375:n2026.
33. Brandwein JM, Zhu N, Kumar R, et al. Treatment of older patients with acute myeloid leukemia (AML): revised Canadian consensus guidelines. Am J Blood Res. 2017;7:30–40.
34. Heuser M, Ofran Y, Boissel N, et al. Acute myeloid leukaemia in adult patients: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31:697–712.
35. Sekeres MA, Guyatt G, Abel G, et al. American society of hematology 2020 guidelines for treating newly diagnosed acute myeloid leukemia in older adults. Blood Adv. 2020;4:3528–3549.
36. United Nations. Available from: https://www.un.org/en/development/desa/population/events/pdf/expert/29/session1/EGM_25Feb2019_S1_SergeiScherbov.pdf. cited 2022 Mar 30.
37. Shlush LI. Age-related clonal hematopoiesis. Blood. 2018;131:496–504.
38. Oliai C, Schiller G. How to address second and therapy-related acute myelogenous leukaemia. Br J Haematol. 2020;188:116–128.
39. Mangaonkar AA, Patnaik MM. Patterns of care and survival for elderly acute myeloid leukemia-challenges and opportunities. Curr Hematol Malig Rep. 2017;12:290–299.
40. Klepin HD. Geriatric perspective: how to assess fitness for chemotherapy in acute myeloid leukemia. Hematology Am Soc Hematol Educ Program. 2014;2014:8–13.
41. Michaelis LC, Klepin HD, Walter RB. Advancements in the management of medically less-fit and older adults with newly diagnosed acute myeloid leukemia. Expert Opin Pharmacother. 2018;19:865–882.
42. Etienne A, Esterni B, Charbonnier A, et al. Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. Cancer. 2007;109:1376–1383.
43. Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106:2912–2919.
44. Giles FJ, Borthakur G, Ravandi F, et al. The haematopoietic cell transplantation comorbidity index score is predictive of early death and survival in patients over 60 years of age receiving induction therapy for acute myeloid leukaemia. Br J Haematol. 2007;136:624–627.
45. Kadia TM, Cortes J, Ravandi F, et al. Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia: a phase 2 single-arm trial. Lancet Haematol. 2018;5:e411–e421.
46. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. Cancer. 2006;106:1090–1098.
47. Kantarjian H, Ravandi F, O'Brien S, et al. Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. Blood. 2010;116:4422–4429.

48. Aydin S, Audisio E, D'Ardia S, et al. Assessment of patients fitness at diagnosis in elderly acute myeloid leukemia. Blood. 2016;128:4012.
• **Good review on fitness assessment.**
49. Aydin S, Franzino M, Frairia C, et al. Assesment of frailty scores validating fitness of elderly AML patients for intensive chemotherapy: a single centre study. Blood. 2018;132:5171.
50. Urbino I, Secreto C, Olivi M, et al. Evolving therapeutic approaches for older patients with acute myeloid leukemia in 2021. Cancers (Basel). 2021;13(20):5075.
51. Sorror ML, Storer BE, Fathi AT, et al. Development and validation of a novel acute myeloid leukemia-composite model to estimate risks of mortality. JAMA Oncol. 2017;3:1675–1682.
52. Malfuson JV, Etienne A, Turlure P, et al. Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. Haematologica. 2008;93:1806–1813.
53. Wheatley K, Brookes CL, Howman AJ, et al. Prognostic factor analysis of the survival of elderly patients with AML in the MRC AML11 and LRF AML14 trials. Br J Haematol. 2009;145:598–605.
54. Krug U, Rollig C, Koschmieder A, et al. Complete remission and early death after intensive chemotherapy in patients aged 60 years or older with acute myeloid leukaemia: a web-based application for prediction of outcomes. Lancet. 2010;376:2000–2008.
55. Walter RB, Othus M, Borthakur G, et al. Prediction of early death after induction therapy for newly diagnosed acute myeloid leukemia with pretreatment risk scores: a novel paradigm for treatment assignment. J Clin Oncol. 2011;29:4417–4423.
56. Soubeyran P, Bellera CA, Gregoire F, et al. Validation of a screening test for elderly patients in oncology. J Clin Oncol. 2008;26:20568.
57. Soubeyran P, Bellera C, Goyard J, et al. Validation of the G8 screening tool in geriatric oncology: the ONCODAGE project. J Clin Oncol. 2011;29:9001.
58. Sherman AE, Motyckova G, Fega KR, et al. Geriatric assessment in older patients with acute myeloid leukemia: a retrospective study of associated treatment and outcomes. Leuk Res. 2013;37:998–1003.
59. Loh KP, Klepin HD. Geriatric assessment in older patients with acute myeloid leukemia. Cancers (Basel). 2018;10(7):225.
60. Klepin HD, Geiger AM, Tooze JA, et al. Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. Blood. 2013;121:4287–4294.
61. Deschler B, Ihorst G, Platzbecker U, et al. Parameters detected by geriatric and quality of life assessment in 195 older patients with myelodysplastic syndromes and acute myeloid leukemia are highly predictive for outcome. Haematologica. 2013;98:208–216.
62. Gratwohl A. The EBMT risk score. Bone Marrow Transplant. 2012;47:749–756.
63. Yanada M, Konuma T, Mizuno S, et al. Predicting non-relapse mortality following allogeneic hematopoietic cell transplantation during first remission of acute myeloid leukemia. Bone Marrow Transplant. 2021;56:387–394.
64. Hegde A, Murthy HS. Frailty: the missing piece of the pre- hematopoietic cell transplantation assessment? Bone Marrow Transplant. 2018;53:3–10.
65. Polverelli N, Tura P, Battipaglia G, et al. Multidimensional geriatric assessment for elderly hematological patients (>/=60 years) submitted to allogeneic stem cell transplantation. A French-Italian 10-year experience on 228 patients. Bone Marrow Transplant. 2020;55:2224–2233.
66. Ferrara F, Barosi G, Venditti A, et al. Consensus-based definition of unfitness to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. Leukemia. 2013;27:997–999.
•• **Consensus-based definition of fitness by the Italian SIE/SIES/GITMO scientific/cooperative gropus.**
67. Palmieri R, Paterno G, De Bellis E, et al. Validation of SIE, Sies, GITMO operational criteria for the definition of fitness in elderly patients affected with acute myeloid leukemia: a six-years retrospective real-life experience. Blood. 2019;134:2150.
68. Palmieri R, Othus M, Halpern AB, et al. Accuracy of SIE/SIES/GITMO consensus criteria for unfitness to predict early mortality after intensive chemotherapy in adults with AML or other high-grade myeloid neoplasm. J Clin Oncol. 2020;38:4163–4174.
69. Borlenghi E, Pagani C, Zappasodi P, et al. Validation of the "fitness criteria" for the treatment of older patients with acute myeloid leukemia: a multicenter study on a series of 699 patients by the Network Rete Ematologica Lombarda (REL). J Geriatr Oncol. 2021;12:550–556.
70. Borlenghi E, Pagani C, Zappasodi P, et al. Secondary acute myeloid leukaemia in elderly patients: patient's fitness criteria and ELN prognostic stratification can be applied to guide treatment decisions. An analysis of 280 patients by the network rete ematologica lombarda (REL). Am J Hematol. 2018;93:E54–E57.
71. Min GJ, Cho BS, Park SS, et al. Geriatric assessment predicts nonfatal toxicities and survival for intensively treated older adults with AML. Blood. 2022;139:1646–1658.
72. Klepin HD. Toward consensus on geriatric assessment in AML. Blood. 2022;139:1605–1606.
73. Vey N. Blurring lines between treatment intensity and patient fitness in elderly people with AML. Lancet Haematol. 2018;5:e383–e384.
74. Chen EC, Garcia JS. Does patient fitness play a role in determining first-line treatment of acute myeloid leukemia? Hematology Am Soc Hematol Educ Program. 2020;2020:41–50.
75. Isidori A, Loscocco F, Visani G. AML therapy in the elderly: a time for a change. Expert Opin Drug Saf. 2016;15:891–892.
76. Zuckerman T, Rowe JM. Shifting therapeutic paradigms in induction and consolidation for older adults with acute myeloid leukemia. Curr Opin Hematol. 2019;26:51–57.
77. Palmieri R, Paterno G, De Bellis E, et al. Therapeutic choice in older patients with acute myeloid leukemia: a matter of fitness. Cancers (Basel). 2020;12(1):120.