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Review Article

Geriatric assessment in older adults with acute myeloid leukemia: A Young International Society of Geriatric Oncology narrative review

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ABSTRACT

The therapeutic landscape of acute myeloid leukemia (AML) in older adults has been transformed by the advent of targeted therapies, including venetoclax (a B-cell lymphoma-2 inhibitor), gilteritinib (a FMS-like tyrosine kinase 3 inhibitor), ivosidenib, and enasidenib (isocitrate dehydrogenase 1/2 inhibitors). These agents, in combination with hypomethylating agents, have significantly improved outcomes among patients aged 60 years and older, however, overall survival remains very poor. Hence, the management of AML in this population requires a nuanced approach to balance overall survival, treatment-related toxicities, quality of life, and the preservation of functional independence.

In recent years, geriatric assessment (GA) has emerged as a critical strategy to identify vulnerabilities that may not be captured in routine oncology evaluations. This assessment helps guide tailored interventions to optimize the fitness of older adults, allowing for better risk stratification and thereby informing treatment plans. This review discusses available evidence for each domain within the GA, feasibility of GA in clinical trials, and gaps in knowledge and future directions to fill those gaps.

1. Background

Principles of geriatric oncology are highly relevant in the management of acute myeloid leukemia (AML), a disease with a median age of diagnosis of 69 years in the United States [1]. The therapeutic landscape of AML has undergone a transformative shift with the advent of novel agents, including venetoclax (a B cell Lymphoma-2 [Bcl-2] inhibitor), gilteritinib (an FMS-like tyrosine kinase 3 inhibitor), ivosidenib, and enasidenib (isocitrate dehydrogenase −1/−2 inhibitors). These innovations have ushered in an era of tailored treatment strategies, leveraging the unique molecular profiles of AML. Despite these advancements, the prognosis for older adults, aged 60 years and above, afflicted with AML is poor. The median overall survival (OS) for older adults ranges from 9.6 to 14.7 months [2]. Consequently, optimizing the delicate balance between enhancing OS, preserving the quality of life, mitigating treatment-related toxicities, and safeguarding functional independence is important in the management of older patients with AML [3,4].

In recent years, dedicated efforts have sought to distinguish individuals with an increased risk of treatment-related toxicities, functional decline, and compromised quality of life while undergoing cancer treatments. Amidst this backdrop the geriatric assessment (GA) has emerged, a comprehensive array of instruments, each tailored to appraise the functional reserves within distinct geriatric domains. GA

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can identify underlying vulnerabilities that are often undetected in routine oncological assessments, facilitate a patient-centered decision-making process, and guide interventions in response to the identified vulnerabilities [5]. This review discusses available evidence for each domain within the GA, feasibility of GA in clinical trials, and gaps in knowledge and future directions to fill those gaps.

2. Methods

A local ethics committee approved this study. The literature search was conducted through Pubmed and Embase, from their inception to July 2024, using the key terms "acute myeloid leukemia" and "geriatric assessment". The screening process was performed through a full-text review. The selection was restrained to those studies including adults older than 60 years old with acute myeloid leukemia. Data on GA, OS, mortality, complete remission (CR), treatment-related toxicities, risk of delirium, and prolonged hospitalizations were collected.

2.1. Characteristics of the Included Studies

Among the 25 studies selected, shown in Table 1, 48 % were cohort studies, 44 % were clinical trials, 4 % were cross-sectional study, and 4 % were systematic reviews. The studies occurred in North America, Europe, and Eastern Asia in 72 %, 16 %, and 12 % of cases, respectively; the more reported timeframes were between 2008 and 2011, and between 2016 and 2020. The median size of the studies was 103 subjects (interquartile ranges [IQR], 71–165). Of interest, the median age in the studies was 70 (IQR, 68–71), with patients undergoing for anthracycline-, hypomethylating agents- (HMA), or venetoclax-based regimens in 80 %, 32 %, and 12 % of cases, respectively. Only one study included patients treated with HMA + venetoclax.

2.2. Geriatric Assessment in AML

The conventional GA domains are comorbidities, physical function, cognition, psychological health, nutritional status, medications, social support, and the presence of geriatric syndromes [6]. The instruments used for geriatric domains are shown in **Table 2**.

2.2.1. Comorbidities

Older adults with AML often have preexisting comorbidities, which are associated with poor outcomes [7,8]. For example, compared to their younger counterparts, older adults with AML had a higher prevalence of diabetes mellitus (19 % vs 8 %), cardiac disease (13 % vs 5 %), and chronic obstructive pulmonary disease (13 % vs. 4 %) [8]. Associations between specific conditions and outcomes in older adults with AML have been reported. In patients treated with anthracycline-based regimens, elevated plasma creatinine levels (>1.3 mg/dL) were independently associated with CR, 8-week induction mortality, and one-year OS (hazard ratio [HR] 1.2, $p = 0.001$) [9]. Moreover, individual comorbidities can influence the selection of treatment regimens. For example, comorbidities such as arterial hypertension, chronic heart failure, coronary artery disease, peripheral artery disease, and chronic renal insufficiency have been shown to be associated with anthracycline-related left ventricular dysfunction [10].

Several index incorporating comorbidities have been developed to help with risk stratification either at diagnosis or prior to hematopoietic stem cell transplantation (HSCT) **(**Table 3**)**. The most used scores in literature were the Transplantation-specific Comorbidity (HCT-CI) and the Charlson Comorbidity Index (CCI), reported in 60 % and in 20 % of studies, respectively. Noteworthy, in patients treated with either HMA or anthracycline-based regimens, an HCT-CI greater than 2 correlated with OS [HR from 1.6, 95 % confidence interval (CI) 1.31–1.95, to 2.5, 95 %CI 1.2–5.2, $p = 0.018$ [11–13]]. Of interest, a single-arm trial explored the value of two comorbidity scores, the Kaplan Feisten Scale (KFS) and CCI, in selecting adults for HSCT [62 % with AML, myelodysplastic syndrome (MDS), or chronic myelogenous leukemia] [14]. In this setting, KFS showed a predictive value on transplanted-related mortality and OS [HR 2.5, $p = 0.038$ [14]]. However, the reliance on chronological age in these scoring systems may lead to both under and over-treatment [15]. Therefore, future models of fitness for older adults with AML seeking to pursue anti-leukemic therapy ought to include GA, which includes comorbidity assessment.

2.2.2. Physical function

Physical function can predict OS and severe toxicities in older patients with AML. Additionally, almost 4 % of older adults value the preservation of their physical function more than being alive one year more or than hematological response, while undergoing treatment [3]. Instruments utilized to assess physical function include the Short Physical Performance Battery (SPPB) [16], Activities of Daily Living (ADLs) assessed with the Katz scale [17], Instrumental Activities of Daily Living (iADLs) assessed with the Lawton scale [18], the Pepper Assessment Tool for Disability (PAT—D) [19], and the Time Up and Go Test (TUGT) [20]. Older patients with AML, at diagnosis, presented with impaired mobility in 69 % of cases as measured by an SPPB of ≤9/12 [21], and in 51 % of cases as measured by a TUGT of >13.5 s [13]. Impairments in ADLs and iADLs, assessed with either PAT-D subscales or Katz and Lawton scales, were present in 23 % to 65 % and in 16 % to 75 %, respectively [21–27]. Among patients treated with anthracycline-based regimens, physical impairment measured by the SPPB was associated with OS [HR from 1.9, 95 %CI 1.1–3.4, $p = 0.027$, to 2.7, 95 %CI 1.2–6.0, $p = 0.018$ [22,23,28]], non-relapse mortality (NRM) ($p = 0.033$) [28], grade 3 to 4 infections ($p = 0.024$) [28], and acute renal failure ($p = 0.013$) [28]. Among patients receiving either anthracycline-based regimens or HMA agents, impaired iADLs at diagnosis were predictive of OS [HR from 3.5, 95 %CI 1.2–10.4, $p = 0.025$, to 4.3, 95 %CI 1.7–10.5, $p = 0.001$ [13,27]].

Data on trajectory of physical function is very limited; it may vary according to the toxicity of the therapy being given. Under HMA-based regimens, 52 % of patients had improved SPPB, assessed 3 months after the treatment initiation [21]. On the other hand, under either HMA- or anthracycline-based regimens, iADLs worsened at three months from diagnosis [21,29]. However, prior to allogeneic HSCT, the SPPB did not significantly change from diagnosis to last visit before HSCT (approximately 6.8 months after diagnosis) [29].

2.2.3. Cognition

Preserved cognitive function enables a better understanding of the treatment protocol, with potentially improved therapeutic adherence and prompt reporting and management of toxicities [15]. A cognitive test evaluates deficits in memory, executive functions, language functions, and attention. Assessment tools, in older adult patients with AML, include the Mini-Mental State Examination (MMSE) [30], the Modified Mini-Mental State Examination (3MS) [31], the Montréal Cognitive Assessment (MoCA) [32], and the Blessed Orientation-Memory-Concentration test (BOMC) [33]. Cognitive impairment occurred in 16 to 69 % of older patients with AML, at diagnosis [13,21–26,28]. In patients treated with HMA-based regimens, cognitive impairment at diagnosis per BOMC (score of ≥4) was associated with worse OS [HR 1.7, 95 %CI 1.0–2.8, $p = 0.048$ [13]]. Similarly, for those with anthracycline-based regimens, those with a 3MS score below 77 at diagnosis showed a worse OS [HR 2.5, 95 %CI 1.2–5.5 [22]], and a median OS of 5.2 months compared to 15.6 months [22]. Beyond survival, an impaired MMSE Korean Version (≤23) was associated with grade 3 to 4 infections ($p = 0.044$) [28], prolonged hospitalization (≥40 days) ($p = 0.005$) [28], and risk of delirium among patients treated with anthracycline-based regimens ($p = 0.004$) [28]. Further, cognitive impairment was associated with physical impairment. For example, patients with an impaired 3MS score at diagnosis experienced a faster decline in SPPB [25]. Longitudinally, 23 % of patients receiving HMA-based regimens experienced decline in cognitive functions, assessed

Table 1
Characteristics of the studies.

Studies	Year	Treatment received	Type of GA	Median OS (months)	Key findings of each GA domain
Cheng et Al. [7]	2023	46 % anthracycline-based, 54 % HMA-based	eFI, HCT-CI, comorbidities.	12.1 for anthracycline based, 2.9 for HMA-based	Baseline eFI category was associated with the type of treatment received ($p < 0.01$)
Tawfik et Al. [8]	2015	Anthracycline-based	BMI, glucose, bilirubin, creatinine, CCI.	NA.	Diabetes is adversely associated with 30-day survival.
Kantarjian et Al. [9]	2015	Anthracycline-based	Bilirubine, creatinine.	5.4 (95 %CI 4.4–6.3)	Creatinine >1.3 mg/dL associated with OS on multivariate analysis, HR 1.2.
Hao et Al. [11]	2022	Anthracycline-based and HMA-based	HCT-CI, CCI.	NA.	Meta-analysisis showed HCTCI 3+ VS less than 3 (HR 1.6 95 % CI 1.3–1.9).
Sherman et Al. [12]	2013	35 % anthracycline-based, 34 % HMA-based, 24 % palliative only.	HCT-CI, number of medications, ADL, BMI.	HCT-CI ≤1 versus >1, 11.8 versus 4.8, $P = 0.008$.	HCT-CI is associated with OS in multivariate analysis (HR 1.9; 95 %CI 1.2–3.1).
Artz et Al. [14]	2006	fludarabine, alemtuzumab, and melphalan before allogeneic HSCT.	CCI, KFS.	16.9	KFS and PS separated high- from low-risk patients, for transplant-related mortality ($P = 0.001$) and enhanced prognostic power over the CCI alone ($p = 0.018$)
Ritchie et Al. [13]	2022	HMA-based	ADL, iADL, number of falls, TUGT, BOMC, number of medications, HCT-CI, MHI-17, MOS, % unintentional weight loss, BMI.	8.0	In multivariate analyses, HCT-CI > 3 and BOMC>4 were associated with shorter OS ($p < 0.05$ each)
Bhatt et Al. [21]	2024	35.7 % HMA-based, 54.4 % Venetoclax-based, 10.2 % anthracycline-based.	MoCA, SPPB, ADL, iADL, HCT-CI, PHQ-9, MNA.	NA	From baseline before treatment to three months later, decline in cognitive function, physical function, and depression score were 22.6 %, 26.8 %, and 37.5 %, respectively.
Klepin et Al. [22]	2013	Anthracycline-based.	3MS, CES—D, DT, PAT—D, ADl, iADL, SPPB, hand grip strength, HCT-CI.	11.0	Association with OS in multivariate analysis for SPPB<9 (HR 2.2, 95 %CI 1.1–4.6) and 3MS < 77 (HR 2.5, 95 %CI 1.2–5.5)
Saad et Al. [23]	2020	Anthracycline-based, at post-remission.	3MS, CES—D, DT, HCT-CI, number of medications, ADL, SPPB, hand grip strength, creatinine, at post-remission.	21.9	Association with OS in multivariate analysis for SPPB<9 (HR 2.7, 95 %CI 1.2–6.0) and CES-D < 16 (HR 2.5, 95 %CI 1.1–5.4)
Klepin et Al. [24]	2011	Anthracycline-based	3MS, CES—D, DT, PAT—D, ADL, iADL, SPPB, grip strength, HCT-CI	NA	Impairments in individual GA measures ranged from 23.7 % to 50 %
Klepin et Al. [25]	2016	Anthracycline-based	PAT-D, ADL, iADL, SPPB, hand grip strength, HCT-CI, 3 MS, CES—D, and DT.	NA	After chemotherapy, iADL worsened (mean 1.4 baseline vs 2.1 follow-up, $P < 0.001$), as did mean SPPB (7.5 vs 5.9, $P = 0.02$), and grip strength ($p < 0.001$ for men; $P = 0.007$ for women).
Jouzier et Al. [26]	2021	Anthracycline-based	ADL, iADL, MNA, MMSE, HCT-CI.	20 (95 %CI 16.3–25.6)	Cognitive, functional, and nutritional status at baseline, HCT-CI had no impact on OS. Nutritional status improved significantly during treatment ($p = 0.041$).
Wedding et Al. [27]	2006	79.4 % anthracycline-based, 20.6 % HMA-based	iADL	15.2 (95 %CI, 10.8–22.3)	In multivariate analysis, iADL <8 significantly predicted OS (HR:4.3, 95 % CI 1.7–10.5, $p = 0.001$).
Min et Al. [28]	2022	Anthracycline-based.	Hand grip strength, SPPB, MMSE, KNU-DESC, short GDS, pHQ-9, DT, MNA.	24.9	Association with OS in multivariate analysis for SPPB <9 (HR 1.9, 95 %CI 1.1–3.4), and short GDS >5 (HR 1.9, 95 %CI 1.0–3.6).
Min et Al. [29]	2023	Anthracycline-based and allo-HSCT	ADL, iADL, SPPB, MMSE, KNU-DESC, shortGDS, MNA, DT, PH-9, HCT-CI.	NA	Persistent impairment in SPPB before allo-HSCT strongly predicted inferior 3-year OS (28.6 % vs. 65.9 %, $p = 0.006$).
El-Jawahri et Al. [42]	2019	50 % anthracycline-based, 50 % HMA-based	HADS, PHQ-9	NA	Patients' depression symptoms did not change over time, while their anxiety symptoms decreased over time ($\beta = -0.08$, $P < 0.001$).
Klepin et Al. [41]	2020	Anthracycline-based	ADL, iADL, TUGT, BOMC, HCT-CI, number of medications, MHI-17, MOS, number of falls and % unintentional weight loss in last 6 months, BMI.	14.9 (95 %CI 12.6–23.3)	Self-reported physical function, mental health, social activity and nutritional parameters worsened after induction.
Elliot et Al. [49]	2014	Anthracycline-based.	Number of comorbidities, HCT-CI, CCI, number of medications, inappropriate medications at admission.	6.4	On multivariate analysis, increased number of medications at diagnosis (≥4 vs. ≤1) was associated with lower OS (HR = 2.1, 95 % CI = 1.1–3.9).
Holmes et Al. [70]	2014	Anthracycline-based and allo-HSCT	HCT-CI, number of medications, MNA, SPPB, ADL, iADL, MOS, HADS, Clock draw test, Trail making test A and B.	NA	G8 had a higher sensitivity for an abnormal GA (69.7 %), and VES-13 had a higher specificity (100 %). Both tools had similar discriminatory ability.
Jamy et Al. [73]*	2021	Anthracycline-based or HMA-based	ADl, iADL, eFI, comorbidities.	NA	40 % discordance between the provider and modified GA for fitness. The results of the modified GA influenced treatment decision making in one third of cases.
Jamy et Al. [74]*	2023	NA	eGA	NA	62.7 % provider concordance with the eGA result and 27 post visit reports indicated that the eGA results influenced the treatment decision.
Aydin et Al. [80]	2023	Anthracycline-based, 27 % allo-HSCT.	G8, HCT-CI.	15 (IQR 6.7–50.5).	In multivariate analysis, G8-score (HR: 2.3, 95 % CI 1.5–3.6, $p < 0.001$), the HCT-CI (HR: 1.9, 95 % CI 1.2–3.1, $p = 0.009$) predicted worse OS.

(*continued on next page*)

Table 1 (*continued*)

Studies	Year	Treatment received	Type of GA	Median OS (months)	Key findings of each GA domain
Fujita et Al. [81]	2023	Anthracycline-based.	G8, CCI, serum albumin.	NA	Multivariate Cox modeling identified G8 score as a significant prognostic factor for OS (HR 0.891, 95 % CI 0.808–0.983).
DuMontier et Al. [83]	2021	NA	MoCA, Clock in box test, ADL, iADL, gait speed, FP, FI. Management of functional status, falls, depression, mood disorders, insomnia, nutrition, and pain.	NA	GA with management did improve the odds of having end of life goals-of-care discussions (odds ratio = 3.1, 95 % CI: 1.0 to 9.4).

Abbreviations: ADL: Activity of Daily Living; allo-HSCT: allogeneic hematopoietic stem cell transplantation; BMI: body mass index; BOMC: Blessed Orientation-Memory-Concentration test; CCI: Charlson Comorbidity Index; CES—D: Center for Epidemiological Studies Depression scale; CI: confidence interval; DT: Distress Thermometer; eFI: electronic Frailty Index; eGA: electronic Geriatric Assessment; GA: geriatric assessment; G8: Geriatric 8 score; HADS: Hospital Anxiety and Depression Scale; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; HMA: hypomethylating agents; HR: hazard ratio; HSCT: hematopoietic stem cell transplantation; iADL: instrumental Activity of Daily Living; KFS: Kaplan Feisten Scale; KNU-DESC: Korean version Nursing Delirium Symptom Checklist; MHI-17: Mental Health Inventory 17; MNA: Mini-Nutritional Assessment; MoCA: Montréal Cognitive Assessment; MOS: Medical Outcome Survey; OS: overall survival; PAT—D: Pepper Assessment Tool for Disability; PHQ-9: Patient Health Questionnaire-9; shortGDS: short Geriatric Depression Scale; SPPB: Short Physical Performance Battery; TUGT: Time Up and Go Test; VES-13: Vulnerable Elders Survey-13; 3MS: Modified Mini-Mental State Examination.

* Only the abstract was available to A.C.

with MoCA, from diagnosis to the three months of treatment [21].

2.2.4. Psychological health

Psychological health in older adults with AML is associated with treatment adherence, quality of life, and overall prognosis [34,35]. Tools used to assess psychological health included Geriatric Depression Scale (GDS) [36], Hospital Anxiety and Depression Scale (HADS) [37], Patient Health Questionnaire-9 (PHQ-9) [38], the Mental Health Inventory 17 (MHI-17) [39], and Center for Epidemiological Studies Depression Scale (CES—D) [40]. Impairment in depression and anxiety tests ranged from 18 % to 64 % and from 36 % to 61 %, respectively, in older patients with AML at diagnosis [21–25,29]. A CES-D score $\geq$ 16 and a Korean GDS short form $\geq$6 predicted poor OS in patients treated with anthracycline-based regimens [HR 2.5, 95 %CI 1.1–5.4, $p = 0.027$, and 1.9, 95 %CI 1.0–3.6, $p = 0.048$, respectively [23,28]].

However, after HMA-based regimens, patients perceived an improvement of depressive symptoms, assessed with the PHQ-9 [21], whereas, depressive symptoms worsened at the end of induction with anthracycline, as assessed by the MHI-17 and the short GDS scale [29,41]. Of note, after either HMA or anthracycline-based regimens, patients experienced a decrease in anxiety, assessed with the HADS, from diagnosis up to six months [42]. Patients with more depressive symptoms before anthracycline-based regimens, assessed with the CES—D, experienced more decline in physical function in 8 weeks [25].

2.2.5. Nutritional status

Impaired nutritional status, measured by a low body mass index (BMI) or an unintentional weight loss, correlates with toxicities of chemotherapy [43], quality of life [44], and OS [43,45]. Nutritional risk in this population can be measured using the patient-generated subjective global assessment (PG-SGA) [46], the Mini-Nutritional Assessment (MNA), and its short form [47], with a reported prevalence of impaired nutrition ranging from 20 % to 61 % [21,26,28,29]. At diagnosis, patients exhibited an average weight loss of 2–3 % of their total body weight over the preceding six months [13,41]. Furthermore, at the end of anthracycline-based regimens, a BMI reduction of approximately 2 kg/m^2 and an unintentional weight loss of 6 % have been observed [41]. Importantly, the MNA has been linked to NRM after anthracycline-based regimens ($p = 0.024$) [28].

2.2.6. Medications

A higher number of medicines may result in drug interactions, leading to a potential reduction in efficacy and increased odds of toxicities from treatments including anthracyclines [48]. At the time of admission for initiating either HMA- or anthracycline-based treatments, older patients took on average between four and eight medicines (range 0–22), with 38 % on more than five medications [12,13,23,49]. During treatment, the number of drugs further increased, with 68 % on more than five medications at the end of induction [49]. Among patients receiving anthracycline-based regimens, the number of medications correlated with CCI ($p < 0.0001$) or HCT-CI ($p < 0.0001$) [49].

Potentially inappropriate medications can be identified with Beers Criteria or STOPP and START criteria [50,51]. According to the Beers Criteria, potentially inappropriate medications increased from 19 % at the time of anthracycline-based treatments to 36 % at the end of induction, with anticholinergic and benzodiazepines being the most frequently prescribed medications [49]. Of note, concomitant use of strong cytochrome P450 (CYP)3 A/P-glycoprotein inhibitors, such as atorvastatin, metformin, pantoprazole, and omeprazole, increases exposure to venetoclax, which is eliminated via the CYP3A metabolism [52,53]. In patients treated with anthracycline-based regimens, more than four medications correlated with 30-day mortality and OS [HR 2.1, 95 %CI 1.1–3.9, [49]], with an incremental risk for each further medication on 30-day mortality risk [49]. More than four medications and those metabolized by CYP3A4 were associated with decreased odds of achieving CR [49].

2.2.7. Social support

Patients spent more than half of their time during chemotherapy at home [54,55]. Therefore, it is important to assess the social isolation of the patients since many older adults have reduced social support, often leading to increased risks of toxicities from treatment. Notably, a supportive social environment allowed for better coordination between patients and caregivers, better adherence to the treatment, early detection of toxicities, and moral support [56–58]. Patients receiving anthracycline-based regimens generally reported a good social support, assessed via the Medical Outcome Survey's (MOS) Social Support Survey [59], with a median score between 93 and 94 out of 100 [13,41], without any significant decline at the end of induction [41]. MOS Social Support survey score was not associated with OS [41]. At diagnosis, among patients receiving either anthracycline based-regimen or HMA agents, reductions in social activities, engagement in their hobbies, and time spent with family, have been reported in 23 %, 30 %, and 13 % of cases, respectively [12].

2.2.8. Geriatric syndromes

Geriatric syndromes are clinical conditions common to older adults which are of multifactorial origin, not one disease entities [60] and are associated with OS [61,62], non-relapse mortality [61], days out of the hospital [63], and hospitalization for toxicity during chemotherapy [64] in older patients with cancer. Falls, delirium, pressure ulcers, incontinence (urinary or fecal), and frailty are common geriatric syndromes. At diagnosis, 18 % of older adults with AML fell at least once in the past six months [22], and 2 % experienced delirium, as detected with the Korean

Table 2
Instruments used for geriatric domains.

Domain	Measurements	Description
Physical Function	Short Physical Performance Battery (SPPB) [16]	**Items:** Standing balance, 4-m gait speed, time to rise from a chair five times. **Score Range:** 0–12. **Interpretation:** Scores <10 independently predict disability in activities of daily living and mobility.
	Time up and go test (TUGT) [20]	**Items:** Stand up from a chair, walk for 3-m, come back to the chair. **Score Range:** ≤10 s is normal, ≤20 s good mobility, >21 s cannot go outside alone. **Interpretation:** A score of ≥14 s has been shown to indicate high risk of falls.
	Activities of Daily Living (ADL) [17]	**Items:** Basic self-care tasks including bathing, dressing, toileting, maintaining continence, grooming, feeding, and transferring. **Interpretation:** ADLs >0 are predictors of admission to nursing homes, need for alternative living arrangements, hospitalization, and use of paid home care.
	Instrumental Activities of Daily Living (IADL) [18]	**Items:** Higher level activities that maintain independence, including shopping for groceries, driving or using public transportation using the telephone, performing housework, doing home repair, preparing meals, doing laundry, taking medications, and handling finances. **Interpretation:** Individuals may require outside assistance to continue living independently if IADLs <8.
	Pepper Assessment Tool for Disability (PAT—D) [19]	**Items:** 23 items that assess ADL, IADL, and mobility. Responses are made on a five-point likert scale ranging from 1 ("usually did with no difficulty") to 5 ("unable to do") with a box that can be checked stating "usually did not do for other reasons." **Score Range:** 19–95. **Interpretation:** Tool to track changes over time. A change in score can trigger a referral to physical therapy.
Cognition	Mini-Mental State Examination (MMSE) [33]	**Items:** 19 items including orientation, verbal memory, concentration and calculation, language, praxis, and visuospatial construction. **Score Range:** 0–30. **Interpretation:** Higher scores indicate better cognitive performance.
	Montréal Cognitive Assessment (MoCA) [32]	**Items:** 11 items including alternating trail making, visuo-constructional skills, naming, memory, attention, verbal fluency, sentence repetition, orientation, delayed recall and abstraction. **Score Range:** 0–30. **Interpretation:** Abnormal score is defined as ≤26 points.
	Modified Mini-Mental State Examination (3MS) [31]	**Items:** Expanded version of MMSE. Includes four additional items (on long-term memory, abstract thinking, category fluency, delayed recall). **Score Range:** 1–100. **Interpretation:** A score ≤ 77 is a positive screen for memory impairment.
	Blessed Orientation-Memory-Concentration test (BOMC) [37]	**Items:** Condensed six verbal questions (time of day, count 20 to 1 backwards, month, year, months backwards, and a memory phrase). **Score Range:** 0–28. **Interpretation:** Score of 1 is given for each incorrect response. A score above 10 is abnormal. Used as an initial screen for possible cognitive impairment.
Psychological Health	Geriatric Depression Scale (GDS) [36]	**Items:** 15 yes/no questions on feelings over the past week. **Score Range:** 0–15. **Interpretation:** Score ≥ 5 suggests depression.
	Hospital Anxiety and Depression Scale (HADS) [37]	**Items:** 14 questions assessing frequency of anxiety and depression symptoms in the past week based on a Likert scale of 0–3. **Score Range:** 0–42. **Interpretation:** 0–7 is normal, 8–10 is borderline, ≥11 is abnormal.
	Patient Health Questionnaire-9 (PHQ-9) [42]	**Items:** Depression symptoms ranked on a 0–3 Likert scale. **Score Range:** 0–27. **Interpretation:** 5–9 is mild depression, 10–14 is moderate, 15–19 is moderately severe, and ≥ 20 is severe.
	Center for Epidemiological Studies Depression Scale (CES-D) [44]	**Items:** 20-items rating the frequency of depressive symptoms over the last week on a Likert scale of 0–3. **Score Range:** 0–60. **Interpretation:** 16 or greater is at risk of clinical depression.
	Distress thermometer (DT)	**Items:** five items about physical, emotional, practical, spiritual et social concerns. **Score Range:** from 0 to 10. **Interpretation:** distress if ≥4.
	Mental Health Inventory 17 (MHI-17) [43]	**Items:** a 38-item measure of psychological distress and well-being, developed for use in general populations **Score Range:** 0–100 **Interpretation:** higher score: better mental health, no consensus defined threshold for impairment.
Nutritional Status	Mini-Nutritional Assessment (MNA) [50]	**Items:** Food intake, weight loss, mobility, recent psychological stress or acute disease, neuropsychological problems, BMI, functional dependence, polymedication, ulcers, oral intakes, dairy products, vegetables and protein intakes, liquid intakes, independence in nourishing, self-assessment of global and nutritional status, calf and biceps perimeters. **Score Range:** 0–30. **Interpretation:** 0–17 is malnourished,17–23,5 is at risk of malnutrition, 24–30 is normal nutritional status.
Medications	Beers Criteria [53]	**Items:** Medications considered potentially inappropriate for use

(*continued on next page*)

Table 2 (*continued*)

Domain	Measurements	Description
		in patients older than 65 years, mostly due to high risk for adverse events. Most recently updated in 2023. **Interpretation:** Providers may modify medication, dose, or frequency if a medication is potentially inappropriate.
	Screening Tool of Older Person Prescriptions (STOPP criteria) [54]	**Items:** Version 3 provides an explicit list of 133 medications that should be stopped in older adults. **Interpretation:** Provider can utilize to minimize drug-related adverse events.
	Screening Tool to Alert doctors to the Right Treatment) (START Criteria) [54]	**Items:** Version 3 provides an explicit list of 57 medications that should be started in older adults. **Interpretation:** Providers can ensure that older adults do not miss out on therapies when they may be indicated and beneficial.
Social Support	Medical Outcome Survey (MOS) Social Support Survey [62]	**Items:** 19-item multidimensional including emotional/ informational support, tangible support, affectionate support, positive social interactions, and overall social support **Interpretation:** 0–100, better score, higher social activity
Geriatric Syndromes	Fried's phenotype model (FP) [68]	**Items:** weight loss, poor hand grip strength, slow gait speed, low physical activity, and self-reported exhaustion. **Interpretation:** Frailty if ≥3 criteria, pre-frail if only 1 or 2 criteria are present.
	electronic Frailty Index (eFI) [7]	**Items:** 54 variables sourced from electronic health records. These encompass a spectrum of data including encounter details, diagnosis codes, laboratory results, medication profiles, and information from medical annual wellness visits. **Interpretation:** a score ≥ 21 is classified as frail, between 10 and 21 pre-frail, ≤10 fit.
	Veteran Affair Frailty Index (VA-FI) [76]	**Items:** Considers 31 health deficits. Calculated as the sum of deficits divided by the total possible deficits of 31. **Interpretation:** Predicts outcomes in Veterans aged 65 years and older. ≤0.10 is nonfrail, >0.10–0.20 is prefrail, >0.20–0.30 is mildly frail, >0.3–0.4 is moderately frail, and > 0.4 is severely frail.
	Electronic Geriatric Assessment (eGA) [74]	**Items:** age, ADL and IADL scales, and CCI, evaluating their prognostic role on OS. **Interpretation:** Patients were categorized as Fit (0), Intermediate Frail [1] or Frail (≥ 2).
	Korean version of the Nursing Delirium Symptom Checklist (KNU-DESC) [28]	**Items:** 5 categories of assessment: disorientation, inappropriate behavior, inappropriate communication, illusions or hallucinations, and psychomotor retardation. **Interpretation:** a score ≥ 2 is accurate for early delirium.
Screening Tool for GA	Geriatric 8 (G8) [78]	**Items:** 8 items including food intake, weight loss, mobility, neuropsychological problems, BMI, number of medications, consideration of health status, and age. **Score Range:** 0–17. **Interpretation:** Higher score indicates a better health status. Score of ≤14 should undergo cGA.
	Vulnerable Elders Survey-13 (VES-13) [79]	**Items:** 4 Items including age, consideration of health status, difficulties in activities of daily living and instrumental activities of daily living. **Score Range:** 0–5 points. **Interpretation:** a score of 3+ vs. 0–2 on the screener identified 32 % of individuals as vulnerable. This vulnerable group had four times the risk of death or functional decline when compared to elders scoring 3 or less.

version of the Nursing Delirium Symptom Checklist (KNU-DESC) score ≥ 2 [28,29].

Frailty consists of diminished reserves across various organ systems, leading to an increased sensitivity to stress. It is often associated with a lack of physical activity, inadequate nutritional intake, and/or the physiologic changes of aging [65]. There are two currently accepted models: the frailty phenotype model (FP) and the frailty index (FI) [66–68]. FP assesses grip strength, fatigue, walking speed, physical activity, and unintentional weight loss [68]; Prior to HSCT, frailty according to FP was reported to occur from 20 to 32 % of older patients [69–71]. On the other hand, FI is derived from the accumulation of deficits over time including disability, diseases, physical and cognitive impairments, psychosocial risk factors, and geriatric syndromes [67,72]. The electronic Frailty Index (eFI), electronic Geriatric Assessment (eGA), or the Veteran Affair Frailty Index (VA-FI), are various established FI [73–77]. At diagnosis, 13–30 % of older patients with AML were frail according to eFI and eGA [7,74]. Additionally, frail patients identified with eFI were more likely to have congestive heart failure [7]. Moreover, VA-FI frail patients have been shown to present worse OS ($p < 0.001$) [75].

2.2.9. *Screening tools for GA*

Lack of time and resources are common barriers for the implementation of GA in clinical practice. Thus, screening tools may be used to select those who benefit the most from GA. The Geriatric-8 (G8) [78] questionnaire and the Vulnerable Elders Survey-13 (VES-13) [79] have been studied as screening tools in older patients with AML. The G8 includes eight inquiries spanning nutritional, cognitive, psychological, and functional domains, as well as the use of medication, and age; it yields a maximum score of 17 with 14 or less indicating impairment. VES-13, on the other hand, focused primarily on physical function. At the first hematology visit, an impaired G8 was found in 79 % of those treated with HMA, and in 46 % of older patients with AML eligibles for HSCT [80]. Among patients undergoing anthracycline-based regimens, G8 at diagnosis correlated with OS [for less than 14, HR 2.0, 95 %CI 1.5–2.8, $p < 0.001$ [80], and as continuous variable, HR 0.9, 95 % CI 0.8–1.0 [81]], and among those eligibles for HSCT, it was associated with a lower median OS (7.8 months vs 20.7 months, $p < 0.001$) [80]. Moreover, regardless of treatment, a linear correlation between G8 and mortality was observed, with the optimal G8 cut-off for predicting mortality being 12.5 (sensitivity 0.74, specificity 0.62) [81]. Among older patients with AML and MDS undergoing HSCT, G8 and VES-13 showed acceptable performances for the detection of two or more geriatric impaired domains, with an area under the curve (AUC) of 0.78

Table 3
Comorbidity scores.

	Scores			
	HCT-CI	CCI	HEMA-4	KFS
Study design: Clinical trials/Cohort studies.	4/10	0/4	0/1	0/1
Data collection: Prospective/retrospective.	11/3	1/3	1/0	1/0
Population: hematological/AML only.	1/13	1/3	1/0	1/0
Number of studies.	14(7,12,13,21–26,29,41,49,70,80)	4(8,14,49,81)	1(89)	1(14)
HR for OS (95 %CI).	From 1.6 (1.3–1.9) [11] to 2.5 (1.2–5.2, p = 0.018) [13]	0.92 (0.6–1.3) [11]	2.3(1.3–4.0) 3.9(2.2–7.0) [89]	2.5, $p = 0.0038$

Abbreviations: CCI: Charlson Comorbidity Index; HCT-CI: Hematopoietic Cell Transplantation-specific Comorbidity Index; HEMA-4: HEMA-4 screening tool; HR: hazard ratio; KFS: Kaplan Feisten Scale; OS: overall survival.

(0.65–0.91), and an AUC of 0.76 (0.65–0.87), respectively [70].

2.2.10. Implementation of GA in clinical practice and clinical trials

In geriatrics, the time required to perform a GA with management ranges from 60 to 120 min, which can be challenging in busy oncology clinics [82]. As such, GA should be tailored based on local resources. Among older patients with AML, GA completion rates were high, ranging between 80 % to 100 % [13,24,28,41,83]. Note that GA generally consists of patient-reported questionnaires and objective measures of physical function and cognition. In the inpatient setting, the median time from admission to GA was three days [28], and the median time of GA completion was 40–44 min [24,28]. In two clinical trials of older patients with AML, the median time of GA completion was 23 min by patients, and 10 min by healthcare professionals [13,41]. When available, geriatrics specialists should deliver GA and their management [83]. In a study utilizing this model, the median time from hematologist to the first geriatrics visit was 36 days, with 80 % of patients attending the first visits, and 54 % attending the second one. The updated American Society of Clinical Oncology guidelines on the assessment and management of vulnerabilities before and during systemic treatment of cancer, including blood cancer, suggest a practical geriatric assessment (PGA) be used instead of using more traditional GA instruments. [84] In

Fig. 1. It shows the GA optimization strategies within each domain [84].

older patients with AML we encourage PGA with management – optimization strategies are shown in Fig. 1 – because it stands out for its speed of execution while keeping a satisfying accuracy.

2.2.11. Gaps and future perspectives

We highlighted the relevance of geriatric domains in older adult patients with AML. However, as the HMA + venetoclax is the current standard of care since 2020, most studies done to date have focused on anthracycline-based regimens and single HMA. Therefore, there is an unmet need of investigating the prognostic impact of GA domains in novel targeted treatments, one ongoing study will evaluate GA in patients treated with azacitidine + venetoclax (NCT05458258). Further, there is a need for the geriatric oncology community to decide conventional measures of GA, as this will facilitate the development of GA-guided interventional trials. The PGA [84] has been proposed to fill that gap: a practical, agreed upon set of measures. Moreover, as previously discussed [21,29], and along with other hematological malignancies [85,86], GA domains seems to be dynamic and often influenced by hematological treatment. Hence, we propose the following future directions: [1] Investigate the association of GA domains with hematological outcomes among patients receiving venetoclax-based regimens and novel targeted treatments; [2] Develop risk stratification scores integrating GA with disease-related factors; [3] Assess the efficacy of GA-guided treatment strategies and supportive care interventions; [4] Evaluate GA in clinical trials as the marker of patient fitness for curative versus non-curative strategies [87]; and [5] Evaluate the cumulative incidence of GA domains, such as frailty, during treatment. To our knowledge, in older adults with AML, one study prospectively assessed the impact of a treatment selection based on GA and AML molecular profiling and has found this approach feasible [88]. Hence, GA domains, especially physical functions and comorbidities, would help with the decision of treatment strategy. In the context of HSCT, GA with management will improve hematological outcomes [71], and one study (NCT05972577) is ongoing to assess whether a geriatric optimization plan improves physical function, rate of complete remissions, mortality, quality of life, rate of grade 3 and 4 toxicities, neurocognitive status, symptoms burden and other impairments detected with GA in older patients with various hematologic malignancies.

In conclusion, GA is feasible and can identify common vulnerabilities in older adults with AML, helping with the risk stratification. Ongoing studies are assessing GA-guided treatment approaches and management of outcomes.

Author Statement

During the preparation of this work the author(s) used CHATGPT 3.5 and DEEPL to improve language and readability. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

CRediT authorship contribution statement

Andrea Sebastiano Ciccone: Writing – original draft, Writing – review & editing, Supervision, Project administration. **Vincent Thibaud:** Writing – original draft, Writing – review & editing. **Kelly Pugh:** Writing – original draft, Writing – review & editing. **Bochra Sedaki:** Writing – original draft. **Vanya Slavova-Boneva:** Writing – original draft. **Adolfo Gonzalez Serrano:** Writing – original draft. **Nina Neuendorff:** Writing – original draft. **Thomas Cluzeau:** Writing – original draft. **Kah Poh Loh:** Conceptualization, Writing – review & editing, Supervision, Project administration.

Declaration of Competing Interest

The authors have no conflict of interest to report.

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