

Correlation of geriatric assessment and outcomes of acute myeloid leukemia in elderly patients

Research Article

Mostafa Kamal El Razzaz, Tamer Mohamed Ahmed, Hebatullah Magdy,
Ramadan Eid Dawod, Basma Saeid Mansour

*Clinical Hematology, Bone Marrow Transplantation Unit, Internal medicine
department, Faculty of Medicine, Ain Shams University*

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Abstract: **Background:** Frailty is a vulnerable susceptibility to stressors during aging. Assessment of frailty could help make appropriate management plans and early interventions. Geriatric 8 (G8) is a screening tool designed to identify those at risk for frailty who need a more detailed assessment, while Geriatric Assessment in Hematology (GAH) is a multidimensional assessment similar to the comprehensive assessment designed specifically for patients with hematological malignancies. **Methods:** Thirty-two newly diagnosed elderly acute myeloid leukemia (AML) patients, with a mean age of 64.9 years, were assessed by G8 and GAH scores to be reclassified into 16 frail patients and 16 non-frail patients. The disease progression, hospital stay, complications, overall survival, and mortality rates in both groups were followed for 6 months. **Results:** Comorbidities with diabetes mellitus (DM) and hypertension (HTN) were significantly higher in frail patients compared to non-frail patients; also, the ECOG performance score was significantly higher in frail patients compared to the non-frail patients. At 6 months of evaluation, non-frail patients had better overall response compared to frail patients, on using both G8 and GAH scores. At 1, 3, and 6 months of evaluation, the frail patients group exhibited a significantly higher mortality rate than the non-frail group. In our study, median hospitalization of non-frail group was significantly higher than that of frail group and total incidence of complications did not reveal a significant correlation with patient's frailty status. **Conclusion:** Based on G8 and GAH scores, frail AML patients were more likely to have a higher incidence of early mortality and lower overall survival compared to non-frail patients.

Keywords: *Frailty • Acute myeloid leukemia • Geriatric 8 (G8) • Geriatric Assessment in Hematology (GAH)*

1. Introduction

Clinical outcome of elderly acute myeloid leukemia (AML) patients is generally frustrating with less than 20% showing 2-year overall survival, due to tumor behavior, poor tolerance to chemotherapy, physical and cognitive function impairment with aging, and high prevalence of comorbidity.^[1]

Frail patients have a vulnerable state due to an age-related impairment in functional and physiological capacity.^[2] Increased vulnerability affects their susceptibility to poor health outcomes such as falls, prolonged and recurrent hospitalization, illness-related complications, disability, and death.^[3]

The main goal of geriatric assessment in hematology patients is tailoring of appropriate management plan by identifying patients who can tolerate the usual chemotherapy doses and frail patients who will benefit from treatment adjustment.^[4]

Geriatric 8 (G8) is a screening tool recommended by the International Society of Geriatric Oncology (SIOG) as a self-administered assessment.^[5,6]

Also, Geriatric Assessment in Hematology (GAH) was introduced by hematology groups and geriatricians as an internally reliable, rapid, and valid scale for evaluation of older hematological patients.^[7]

* E-mail: Mostafa Kamal El Razzaz

1.1. Aim of the work

To study if geriatric assessment using G8 and GAH can be of value in the initial workup of elderly acute leukemia patients and if their use can be independently correlated with mortality or morbidity.

2. Subjects and Methods

2.1. Patient Selection

A prospective cohort study was conducted in the Hematology Unit of Internal Medicine Department at Ain Shams University Hospital between June 2022 and March 2023. It was conducted in conformity with the standards of the ethical committee of Faculty of Medicine, Ain Shams University, Cairo, Egypt. An informed consent was obtained from all subjects in the study.

The study included 32 newly diagnosed AML patients aged ≥ 60 years, taking into consideration the retirement age in Egypt, which is 60 years.^[8,9] Then, patients were subdivided into two groups (frail patients and non-frail patients) using G8 and GAH scores.

2.2. Study Tools

G8 questionnaire: It consists of eight items covering multiple geriatric assessment domains (appetite

changes, weight loss, mobility, neuropsychological problems, body mass index, medication, self-reported health, and patient age). Overall, the G8 score ranges from 0 (heavily impaired) to 17 (not at all impaired), with a cutoff for potential frailty of ≤ 14 (**Fig. 1**).^[10]

The **GAH scale**, described by **Bonanad et al. (2015)**, has eight scale dimensions (number of drugs, gait speed, mood, activities of daily living, subjective health status, nutrition, mental status, and comorbidity) (**Fig. 2**).^[7] The optimal cutoff point for the GAH scale that indicates high risk of toxicity was 42, with 68.5% sensitivity and 55.8% specificity.^[11]

2.3. Study Procedures

All recruited patients were assessed by thorough medical history, full clinical examination, laboratory investigations including complete blood count with differential, liver and kidney function tests, lactate dehydrogenase (LDH), viral screening tests (HBsAg, HCVAb, and human immunodeficiency virus antibodies [HIV Abs]), bone marrow aspiration, immunophenotyping, and cytogenetics. Echo cardiography was done for all patients as well.

Frailty was initially assessed according to both G8 and GAH scores by a trained hematologist physician.

Patients were followed up regarding treatment outcome, occurrence of complications, and mortality rates for 6 months following initial diagnosis.

Items	Score
Has food intake declined over the past 3 months due to loss of appetite, digestive problems, chewing, or swallowing difficulties?	0 : severe decrease in food intake 1 : moderate decrease in food intake 2 : no decrease in food intake
Weight loss during the last 3 months	0 : weight loss > 3 kg 1 : does not know 2 : weight loss between 1 and 3 kgs 3 : no weight loss
Mobility	0 : bed or chair bound 1 : able to get out of bed but does not go out 2 : goes out
Neuropsychological problems	0 : severe dementia or depression 1 : mild dementia or depression 2 : no psychological problems
Body mass index (BMI) (weight in kg) / (height in m ²)	0 : BMI < 19 1 : BMI = 19 to BMI < 21 2 : BMI = 21 to BMI < 23 3 : BMI = 23 and > 23
Takes more than 3 medications per day	0 : yes 1 : no
In comparison with other people of the same age, how does the patient consider his/her health status?	0 : not as good 0.5 : does not know 1 : as good 2 : better
Age	0 : > 85 1 : 80 - 85 2 : < 80
Total score	0-17

Figure 1: G8 score.

Dimension	Measurement	Range of score	Cut-off point (1 point)
No. Of drugs	Medication count of drugs of current use.	Continuous	≥ 15
Gait speed	Double determination of gait speed at usual pace over a 4 meter course	Continuous	< 0.8 m/s
Mood	single item from the CES-D; In the last week, did you feel depressed?	Never, rarely, or occasionally (no more than 2 days); frequently, most of the time or all time (3-7 days)	Frequently, most of the time or all time (3-7 days)
Activities of daily living	Item no. 4 of the VES-13 instrument; Do you have any difficulty in ... ? Do you need any help in your daily living? Do you have a caregiver?	Yes/ No	Needs help in at least one area
Subjective health status	Single item from VES-13 instrument; Compared to other people your age, would you say your health is ... ?	Poor, fair, good, very good, or excellent	Poor and fair
Nutrition	Four items from the MNA-SF; BMI, weight loss during the last 3 months, and psychological stress or acute disease.	0-10	≤ 8
Mental status	SPMSQ	Right/ wrong	≥ 3 errors
Comorbidities	Prognostic index for 4- year mortality in older adults	0, for absence; 1, for DM or BMI < 25 kg/m ² ; 2, for cancer, lung disease, heart failure, or smoking habit	≥ 3

BMI; body mass index, CES-D; Center for Epidemiological studies Depression Scale, MNA-SF; Mini assessment questionnaire, SPMSQ; short portable mental status questionnaire, VES-13; 13 item vulnerable elderly survey

Figure 2: GAH score.

Response criteria were defined according to European Leukemia Net (ELN) recommendations.^[12]

2.4. Statistical Analysis

The collected data were coded and managed by IBM Statistical Package for Social Sciences (SPSS), version 23. Parametric data were presented as mean, standard deviations and ranges, while nonparametric data were presented as median and interquartile range (IQR). Also, qualitative data were added as number and percentages. Chi-square test was used in the comparison of any introduced qualitative data. Independent *t*-test was used for those with quantitative data and parametric distribution, while Mann–Whitney test was used to compare between two groups with quantitative data and nonparametric distribution. Spearman correlation coefficients were used to assess any correlation between two quantitative parameters in the same group. Confidence intervals were set to 95%, and the accepted margin of error was set to 5%. *P*-values > 0.05 were considered nonsignificant, while $P < 0.05$ was considered significant and $P < 0.01$ was considered highly significant.

3. Results

Our study included 32 newly diagnosed elderly AML patients with a mean age of 64.9 years (60–86). Half

of our patients were frail ($n = 16$) and half of them were non-frail on assessment by using G8 and GAH scores. The mean age was significantly high in the frail group compared to the non-frail group (67.3 years in the frail group vs. 62.5 years in the non-frail group, *P*-value 0.016). Comorbidities with DM and HTN were significantly higher in frail patients compared to non-frail patients (*P*-values 0.033 and 0.012, respectively). Our patients were categorized as diabetic if their fasting plasma glucose was ≥ 126 mg/dL, 2-h plasma glucose was ≥ 200 mg/dL, or glycated hemoglobin (HbA1c) was $\geq 6.5\%$. Also, they were considered hypertensive if the blood pressure was ≥ 130 and/or ≥ 80 mmHg.^[13,14]

According to NCCN guidelines^[15], 23 of our patients had intermediate-risk category (79.3%), five patients had favorable risk (17.24%), while only one patient had adverse risk (3.44%). Such a cytogenetic risk stratification did not reveal a statistical significance with patients' frailty status (**Table 1**).

(2 + 5) was the most common protocol used in our study, applied for 10 patients (31.25%), while oral etoposide and (2 + 7) were the least used protocols (each one was given only to a single patient) (**Table 2**). Azacitidine was not administered to our patients due to financial constraints as all the recruited patients were uninsured.

In our study, incidence of complications (neutropenic fever, pneumonia, abscess, or sepsis) revealed no significant correlation with patient's frailty status. The ECOG performance score was significantly higher in frail patients compared to non-frail patients (*P*-value

Table 1: Comparison between frail and non-frail patient regarding demographic data, comorbidities and risk category.

No. = 32		Total	NF	F	Test value	P-value	Sig.
		No. = 16	No. = 16				
Age	Mean $\pm$ SD	64.94 $\pm$ 6.14	62.56 $\pm$ 3.93	67.31 $\pm$ 7.1	-2.566*	0.016	S
	Range	60 – 86	60 – 75	60 – 86			
DM	No	25 (78.1%)	15 (93.8%)	10 (62.5%)	4.571*	0.033	S
	Yes	7 (21.9%)	1 (6.2%)	6 (37.5%)			
HTN	No	13 (40.6%)	10 (62.5%)	3 (18.8%)	6.348*	0.012	S
	Yes	19 (59.4%)	6 (37.5%)	13 (81.2%)			
Viral hepatitis	No	29 (90.6%)	14 (87.5%)	15 (93.8%)	0.368*	0.544	NS
	Yes	3 (9.4%)	2 (12.5%)	1 (6.3%)			
Cytogenetics	Favorable	5 (17.2%)	1 (6.2%)	4 (30.8%)	4.670*	0.097	NS
	Intermediate	23 (79.3%)	15 (93.8%)	8 (61.5%)			
	Adverse	1 (3.4%)	0 (0.0%)	1 (7.7%)			

Table 2: Treatment protocols used in all patients.

Treatment Protocol	Total	Percentage	F	NF
2+5	10	31.25%	4	6
2+7	1	3.12%	0	1
3+7	7	21.87%	0	7
Oral Etoposide	1	3.12%	1	0
PETHEMA Induction	4	12.5%	3	1
S/C Cytarabine	6	18.75%	5	1
Supportive Treatment	3	9.37%	3	0

<0.001). The median hospitalization of non-frail group was significantly higher than that of frail group (P -value 0.009) (Table 3).

At 1 month, the overall response in patients who received induction treatment ($n = 22$) was (63.63%), with seven patients showing complete response (31.8%) and seven patients showing partial response (31.8%).

Early mortality occurred in five out of 32 patients (15.6%), while mortality at 6 months reached 53.1%. Mortality was significantly correlated with the cytogenetic risk in the period of follow-up, being higher in adverse cytogenetic risk group compared to the intermediate and favorable cytogenetic risk groups ($P < 0.001$).

Response to treatment at 1 month showed a significant statistical difference between both frail and non-frail groups on using the G8 and GAH scores (P -value 0.002). CR and PR rates were higher in non-frail group, while resistance and mortality rate were higher in frail group. Mortality at 3 and 6 months follow-up was significantly higher in frail group when compared to the non-frail group on using both G8 and GAH scores, with a P -value of 0.001 (Table 4).

The 6-months survival curve showed a significantly better survival in non-frail group compared to frail group on using both G8 and GAH scores (Figs 3, 4).

4. Discussion

In our study, we included 32 elderly AML patients who were 60 years or older, according to the Egyptian census definition of the elderly population, and reclassified them as frail and non-frail using G8 and GAH scores.^[16] It was found that the mean age of frail patients was significantly higher. This is supported by *Atakul and Akyar's 2019* study, which involved 90 patients with hematological diseases, who were aged 65 years or older. The study found that women aged 75 years and older were more likely to be frail than those who were younger. The researchers used a modified version of the Edmonton Frailty Scale to assess frailty.^[17]

Comorbidities with DM and HTN were significantly higher in frail patients compared to non-frail patients (P -values 0.033 and 0.012, respectively). In line with our results, *Vetrano et al. (2018)* and *García-de-Alba-García et al. (2020)* reported that frailty and prefrailty are observed more in patients with DM and HTN.^[18, 19]

In our study, hospitalization days were higher in non-frail patients and the total incidence of complications did not reveal a significant difference between frail and non-frail patients. This is different from the results of *Gi-June Min et al. (2023)*, who studied elderly patients with a median age of 63 years. They found that frail patients had a higher incidence of prolonged hospitalization days (≥ 40) in their study ($P = 0.005$). In addition, frail patients had a significantly higher incidence of nonfatal toxicities ($P = 0.044$). (20) It is possible that the high mortality rate of our frail patients caused their hospitalization to be shorter, resulting in a lower overall incidence of complications in the frail group compared to the non-frail group.

Also, this could be attributed to treatment schedule as more aggressive treatment protocols (e.g., 3 + 7 protocol) were more frequently used in non-frail patients, while less-aggressive protocols (such as oral etoposide

Table 3: Comparison between frail and non-frail patient regarding incidence of complications, ECOG performance and hospitalization.

Total no. = 32		Total NF	F		Test value	P-value
		No. = 16	No. = 16			
Complications	NF	21 (65.6%)	10 (62.5%)	11 (68.8%)	0.139*	0.710
	Pneumonia	8 (25.0%)	6 (37.5%)	2 (12.5%)	2.667*	0.102
	Abscess	7 (21.9%)	4 (25.0%)	3 (18.8%)	0.183*	0.669
	Sepsis	7 (21.9%)	2 (12.5%)	5 (31.2%)	1.646*	0.200
ECOG score	Median (IQR)	1 (0 – 2)	0 (0 – 1)	2 (2 – 3)	-4.589#	<0.001
	Range	0 – 4	0 – 1	1 – 4		
Hospitalization	Median (IQR)	22.5 (17 – 31.5)	27.5 (21.5 – 33)	17.5 (11 – 23)	-2.603#	0.009
	Range	5 – 60	15 – 60	5 – 50		

Table 4: Comparison between frail and non-frail patient regarding survival at one month, three and six months.

NF No. (%)		F		Test value	P-value
		No. (%)			
Re-evaluation after one month	CR	7 (43.8%)	0 (0.0%)	15.209	0.002
	PR	5 (31.2%)	2 (12.5%)		
	R	4 (25.0%)	9 (56.2%)		
	Died	0 (0.0%)	5 (31.2%)		
Re-evaluation after 3 months	Alive	16 (100.0%)	7 (43.8%)	12.522	<0.001
	Died	0 (0.0%)	9 (56.2%)		
Re-evaluation after 6 months	Alive	12 (75.0%)	3 (18.8%)	10.165	0.001
	Died	4 (25.0%)	13 (81.2%)		

CR; complete remission, PR; partial remission, R; resistance

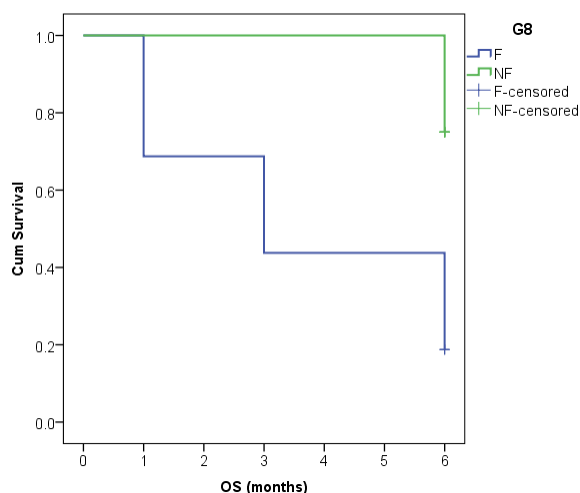


Figure 3: Cumulative survival curve in frail and non-frail patients using G8 score.

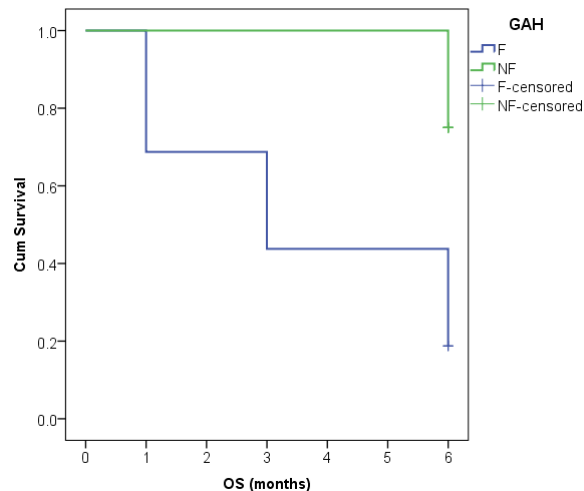


Figure (4): Cumulative survival curve in frail and non-frail patients using GAH score.

and S/C cytarabine) were used more frequently in frail patients (Table 2).

It is worth noting that our study had a relatively small number of patients compared to other studies. For example, *Petrov et al. (2022)* conducted their study on 237 AML patients, while *Lee et al. (2022)* included 1166

veterans with newly diagnosed AML in their study. Both studies reported that frail patients had higher rates of intensive care unit (ICU) admissions.^[21, 22]

According to our results, the 6-month overall survival was significantly better in the non-frail group compared to the frail group on using both G8 and GAH scores.

Like our results, **Umit et al. (2018)** showed that both G8 and VES13 scores has strong survival prediction ($P = 0.001$).^[23]

Also, in concordance with our results, **Gi-June Min et al. (2023)** found that decreased physical functions by short physical performance battery (SPPB) and depressive symptoms by the Korean version of the short form of geriatric depression scales (SGDS-K) were significantly associated with low survival rate, while gait speed and sit-and-stand speed were very useful measurements for survival outcome prediction.^[20]

Also, in accordance with our results, **Budziszewska et al. (2015)**, who conducted their study in 509 elderly AML patients, found that fit patients showed a significantly long overall survival than frail subjects ($P < 0.05$).^[24]

Similarly, **Klepin et al. (2013)** conducted their study on 74 elderly AML patients and found that frail patients with low baseline physical performance have an overall survival of 6.0 months, compared to 16.8 months in patients with better physical performance ($P = .018$).^[25]

Among 87 hospitalized older adults with different clinical diagnoses such as heart failure, chronic obstructive lung disease, pneumonia or stroke, **Volpato et al. (2011)** found that frail patients with moderate physical impairment (with an SPPB score 5–7) had 2.6 times higher risk of death or recurrent hospitalization than non-frail patients.^[26]

This study has some limitations. The small sample size may have affected our results, so further large-scale studies with more elderly patients are essential to establish our results.

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5. Conclusion

The main goal of geriatric assessment in patients with hematological malignancies is to guide therapeutic decisions by identifying fit patients, who can tolerate standard treatment, and frail patients, who may benefit from adjustments of therapy. So, a comprehensive assessment is recommended for proper management of such patients.

Based on G8 and GAH scores, frail patients were more susceptible to a higher incidence of early mortality and lower overall survival compared to non-frail patients.

Frailty scores (G8 and GAH) and adverse risk cytogenetics were independent predictors of response at 1 month and overall survival at 6 months, irrespective to the ECOG performance score.

Our findings support using the G8 and GAH scores as a feasible frailty assessment tool in the initial assessment of newly diagnosed elderly AML patients. Both scores were independent prognostic predictors in elderly AML patients.

Abbreviations

AML (acute myeloid leukemia), ELN (European Leukemia Net), G8 (Geriatric 8), GAH (Geriatric Assessment in Hematology), SIOG (the International Society of Geriatric Oncology), SPPB (short physical performance battery), SGDS-K (short form of the Geriatric Depression Scale-Korean version), DM (diabetes mellitus), HTN (hypertension).

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