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Research Paper

Geriatric assessment in hematology scale predicts treatment tolerability in older patients diagnosed with hematological malignancies: The RETROGAH study

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ABSTRACT

Introduction: The GAH (Geriatric Assessment in Hematology) scale is a psychometrically valid tool aimed at identifying older patients with hematological malignancies at higher risk of treatment-related toxicity. Our objective in this study was to determine the weights for each dimension of the GAH scale and the cut-off point to reliably predict treatment tolerability in this population, estimated by a weighted receiver operating characteristic (ROC) analysis and quantified by the area under the curve (AUC).

Material and Methods: The RETROGAH was a retrospective cohort study including 126 patients who had previously participated in the GAH study. Patients were ≥ 65 years old with newly diagnosed myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), multiple myeloma (MM), or chronic lymphoid leukemia (CLL) and treated with standard front-line therapy within three months after having completed the GAH scale.

Results: The optimal cut-off value of the GAH total score to discriminate patients at higher risk of treatment toxicity was 42, with 68.5% sensitivity and 55.8% specificity. Using this value, 66.1% of patients evaluated were found to develop some type of toxicity. The AUC was 0.6259 (95% CI: 0.512–0.739; $p = 0.035$).

Discussion: The GAH scale not only would enable clinicians to individualize therapy based on individual risk of toxicity but also discriminate patients that will benefit most from intensive treatments from those requiring an

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adapted approach. While futures studies in clinical practice may improve the model and overcome its limitations, the GAH scale should not be used alone when making treatment decisions.

1. Introduction

Malignant disease occurs across all ages, but malignant hemopathies disproportionally affect individuals aged 65 years or older. This tendency will continue to increase in the future [1] as a result of the growing life expectancy and aging of the population. Despite these factors, older patients are under-represented in clinical trials, making it difficult to incorporate evidence-based clinical decisions for this population [2].

The ideal scenario in clinical practice should be to administer standard cancer treatment to as many patients as possible. Regimens with lower dose or less toxic drugs are, however, frequently used in older patients, even when they are less effective or not evidence-based, simply because they are old or seem frail, without sound clinical justification.

Geriatric assessment (GA) identifies older patients with cancer at greatest risk of chemotherapy toxicity and mortality [3–6], and influences decisions about treatment [7–9]. In hematological malignancies, especially in multiple myeloma (MM), there are validated tools for identifying high-risk populations on the basis of geriatric and disease predictors. The International Myeloma Working Group (IMWG) [10] focuses on age, comorbidities, activities of daily living (ADL), and instrumental ADL (IADL) for patients older than 65 years with newly diagnosed multiple myeloma (MM) from clinical trials. The IMWG score was found to predict mortality and the risk of nonhematologic toxicities. The Freiburg Comorbidity Index (I-MCI) [11], based on Karnofsky performance status (PS), lung disease, and renal disease, is predictive of survival in patients with MM regardless of age, therapy, and disease stage [12]. The Revised Myeloma Comorbidity Index (R-MCI) also includes age, frailty, and cytogenetics, and had a strong correlation with overall survival (OS) among patients who are frail [13].

The Geriatric Assessment in Hematology (GAH) scoring system developed by Bonanad et al. [14] is an easy instrument that takes approximately 10–12 min that addresses the geriatric dimensions recommended in a GA such as functional, mental and nutritional status, comorbidity, and mobility. The GAH scale has shown to be psychometrically valid [14] and responsive to clinical change [15]. Increasing deficits detected with this tool have been associated with survival outcomes in older patients newly diagnosed with hematologic malignancy [14,16].

In this study, we aimed to determine the weights for each dimension of the GAH scale and the cut-off point that best identify patients at risk for treatment toxicity.

2. Material and Methods

2.1. Study Design and Population

The RETROGAH was a multicentre and retrospective study conducted in fourteen Hematology Units in Spain. This study included older patients (≥ 65 years) who had previously participated in the GAH study [14] with newly diagnosed myelodysplastic syndrome (MDS)/acute myeloid leukemia (AML), MM, or chronic lymphoid leukemia (CLL). Participating patients were also required to have received standard front-line treatment within three months of completing the GAH scale and to give written informed consent if they were still alive at the time of the study.

The study was approved by the Ethics Committee of the Hospital Universitario de la Ribera, Alzira (Valencia, Spain), including a waiver of informed consent for deceased patients.

2.2. GAH Scale and Procedures

Characteristics of the GAH scale have been published [14,15]. Briefly, this is a 30-item tool grouped into eight relevant geriatric dimensions: number of drugs taken, gait speed, mood (based on the Centre for Epidemiological Studies Depression Scale, CES—D), ADL, subjective health status (based on the Vulnerable Elders Survey Instrument-13, VES-13), nutrition (based on the Mini Nutritional Assessment Short Form, MNA®-SF), mental status (based on the Short Portable Mental Status Questionnaire, SPMSQ), and comorbidities. Initially, for exploratory purposes of determining the psychometric properties of the GAH scale, all domains were dichotomized equally (0 or 1) depending on whether the patient scored outside the cut-off value or not (Table 1), generating a single summated score that ranged from 0 to 8, where higher scores represented worse state. Here we report on the score ranging and the optimal cut-off point on the GAH scale that predicts poor tolerance.

For this study, 'treatment modifications' were defined as any of the

Table 1
Characteristics of the 97 evaluable participants.

Characteristic	Value
Age, years (median and range)	78.0 (73.0–83.0)
Sex, n (%)	
Male	44 (45.4)
Female	53 (54.6)
Diagnosis, n (%)	
MDS/AML	47 (48.5)
MM	45 (46.4)
CLL	5 (5.2)
Survival status at study initiation, n (%)	
Alive	30 (30.9)
Dead	67 (69.1)
Causes of death, n (%) ($n = 57$) *	
Disease related	43 (75.4)
Non-disease related	14 (24.6)
GAH items, n (%)	
Number of drugs	
<5	49 (50.5)
≥5	48 (49.5)
Gait speed (m/s)	
≥0.8	26 (26.8)
<0.8	71 (73.2)
Mood (CES-D)	
Felt depressed ≤2 days	68 (70.1)
Felt depressed 3–7 days	29 (29.9)
ADL	
No dependence	58 (59.8)
Any dependence	39 (40.2)
Subjective health status (VES-13)	
Good, very good or excellent	54 (55.7)
Poor and fair	43 (44.3)
Nutrition (MNA-SF)	
>8	38 (39.2)
≤8	59 (60.8)
Mental status (SPMSQ)	
<3 errors	77 (79.4)
≥3 errors	20 (20.6)
Comorbidities	
<3	77 (79.4)
≥3	20 (20.6)

Abbreviations: ADL, activities of daily living; AML, acute myeloblastic leukemia; CES—D, Centre for Epidemiological Studies Depression Scale; CLL, chronic lymphocytic leukemia; MDS, myelodysplastic syndrome; MM multiple myeloma; MNA-SF, Short version of the complete Mini-Nutritional Assessment questionnaire; SPMSQ, Short Portable Mental Status Questionnaire; VES-13, Vulnerable Elders Survey Instrument. *Missing data, $n = 10$.

following: dose reduction/interruption, cycles reduced or delayed, and additional supportive care therapy to cover symptomatic management and possible complications and side effects. Patients receiving any front-line regimen with adjustments based on clinical judgement were excluded from the analysis; we only included those patients who received planned standard therapy and for whom hematologists made treatment decisions to address chemotherapy toxicity.

Patient and disease characteristics, survival status, GAH scores, treatment modifications, and drug-related toxicity were collected by retrospective chart review; the chemotherapy regimens administered and grades of toxicity were not.

2.3. Statistical Analysis

Sample size was based on the theories about the minimum number of observations per variable necessary in regression analysis to evaluate the coefficients for each dimension of the GAH scale. Assuming the ten or fifteen patients per number of predictors that many researchers [17,18] have argued, the number of patients planned to be included ranged from 80 to 120 patients to ensure at least ten patients per item comprised in the GAH scale. We agreed on a minimum sample size of 80 patients.

Data analyses were performed with the Statistical Package for the Social Sciences (SPSS) v18.0 (SPSS, Inc., Chicago, IL, USA). Patient characteristics were described by normally distributed continuous variables expressed as mean ± standard deviation (SD), and categorical ones as absolute number (n) and percentage (%). When an inferential analysis was required, for variables not fitting a normal (or parametric) distribution, the Mann-Whitney test or Kruskal-Wallis tests were used. For variables fitting a normal (or parametric) distribution, the *t*-test or ANOVA were used. In contingency tables for categorical variables, the Fisher's or chi-square tests were used. All hypothesis tests were two-sided and with a significance level of 0.05.

The algorithm for the GAH score that predicts treatment tolerability was determined by calculating a logistic regression model and a full multiple linear regression model, including the corresponding weighting-coefficients, for which the effect variable was the occurrence or not of any toxicity requiring modifications of the initially planned therapy. The receiver operating characteristic (ROC) curve analysis assessing the area under the curve (AUC) was used to calculate sensitivity and specificity at different cut-off points, and the positive and negative predictive values with their respective 95% confidence intervals (CI).

The method applied for determining the optimal cut-off value was the maximum value for the Youden's index (J = 0.243) which is obtained from the ROC curve analysis as the point that maximizes the sum of sensitivity plus specificity (J = sensitivity + specificity - 1).

3. Results

3.1. Study Participants

Of 126 participants who were enrolled, eighteen were screen failures (twelve patients did not receive any treatment, four patients did not meet the inclusion criteria, one patient had incoherent data, and one patient had missing data in one dimension of the GAH scale) and eleven were not included in the analysis because the treating physician decided to make some modifications to the standard front-line therapy before treatment initiation (Fig. 1). The remaining 97 participants who received the therapeutic regimen as initially planned comprised the evaluable population (women, 54.6%; median age [interquartile range, IQR] 78 [73–83] years). Demographic and clinical characteristics of these 97 participants are shown in Table 1.

Overall, 54 (55.7%) participants developed some treatment-related toxicity requiring discontinuation or changes in the planned therapy (Table 2) and 33 out of the 54 were hospitalized due to therapy-related side effects. The most commonly reported treatment-related toxicities were hematologic (42.6%), infections (31.5%), and gastrointestinal disturbances (25.9%).).

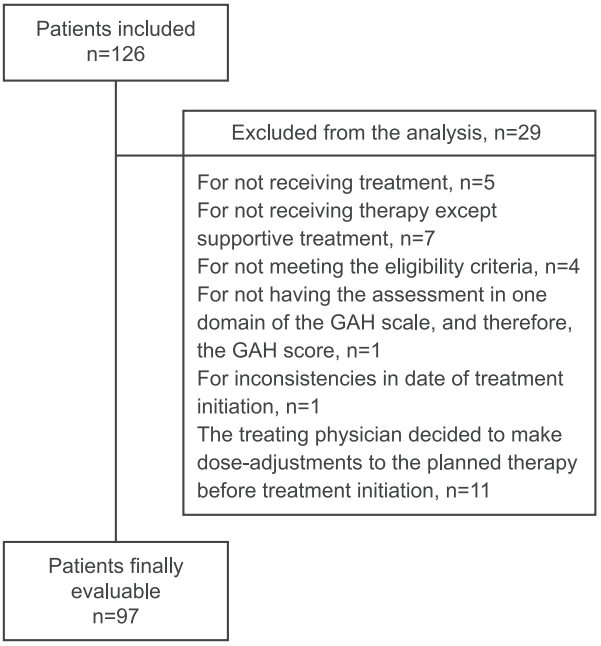


Fig. 1. Patient disposition.

Table 2
Interventions on discontinuation or dosage adjustments of the initially planned therapy due to treatment-related toxicities ($N = 54$).

Intervention*	n (%)
Dose reduction	24 (44.4)
Delay in the administration of treatment cycles	22 (40.7)
Elimination of a drug of the selected schedule	12 (22.2)
Reduction in the number of cycles	9 (16.7)
Supportive care	6 (11.1)
Treatment discontinuation	5 (9.3)
Other	2 (3.7)

* Multiple response possible.

3.2. GAH Scale: Determination of the Final Score and Cutoff Point for Predicting Treatment-Related Toxicity

As shown in Table 3, the weights used to build the GAH score for predicting treatment-related toxicity were obtained from a multiple linear regression analysis following a model bivariate logistic regression, showing a scoring range between 0 and 94 points. Gait speed, ADLs, and nutrition were the only domains retained in the multivariate model as associated risk factors for developing treatment-related toxicity (Table 4). Table 5 shows sensitivity and specificity estimates for selected scores, and Fig. 2 illustrates the ROC curve with AUC for the GAH scale. The AUC was 0.625 (95% CI: 0.512–0.739; $p = 0.035$). The optimal cutoff point for the GAH scale that indicates high risk of toxicity was 42, with 68.5% sensitivity and 55.8% specificity. With this cutoff, the probability that a participant with a GAH score > 42 experienced toxicity (i.e., positive predictive value) was 66.1% and the probability that participants did not have toxicity given a GAH score < 42 (i.e., negative predictive value) was 58.5% (Table 4). Overall, 56 (58%) and 41 (42%) participants had a GAH score > 42 and ≤ 42, respectively. Finally, 37 participants (66.1%) with a GAH score > 42 developed some toxic effects, while only seventeen (41.4%) participants with a GAH score ≤ 42 did. Supplementary Table 1 shows examples of how to

Table 3
Dimensions, cutoff points, and weights for the GAH score.

Dimension	Measurement	Scoring range	Cutoff point (1 point)	Weights for the GAH score
No. of drugs	Medication count of drugs of current use	Continuous	≥ 5	2
Gait speed	Double determination of gait speed at usual pace over a 4-m course	Continuous	< 0.8 m/s	13
Mood	Single item from the Depression Scale of the CES-D	Never, rarely, or occasionally (no >2 days); frequently, most of the time or all time (3–7 days)	Frequently, most of the time or all time (3–7 days)	4
ADL	Item no. 4 of the VES-13 Instrument, and two additional questions.	Yes / No	Needs help in at least one area	22
Subjective Health Status	Single item from the VES-13 Instrument	Poor, fair, good, very good, or excellent	Poor and fair	6
Nutrition	Some items from the MNA-SF	(0–10)	≤ 8	40
Mental Status	SPMSQ	Right / Wrong	≥ 3 errors	2
Comorbidities	Prognostic Index for 4-year Mortality in Older Adults	0–10	≥ 3	5

Abbreviations: ADL, activities of daily living; CES—D, Centre for Epidemiological Studies Depression Scale; MNA-SF, Short version of the complete Mini-Nutritional Assessment questionnaire; SPMSQ, Short Portable Mental Status Questionnaire; VES-13, Vulnerable Elders Survey Instrument.

calculate the GAH score in three geriatric scenarios.

4. Discussion

This study is the first to report on the prognostic value of the GAH scale for predicting treatment-related toxicity in a heterogeneous population of older patients with different newly diagnosed hematological malignancies. By excluding patients with treatment adjustments made based on clinical judgement from our data set, the analysis showed that the cut-off point with the best diagnostic accuracy for the GAH scale was 42. The goal was to design and develop a generic model applicable to several conditions and treatments, therefore promoting the potential applicability in clinical practice. Results of the prospective studies currently conducted in specific subpopulations, such as the QoLMMBuS and GEM-FIT studies (not published), will show whether there are differences in predicting toxicity when the cut-off of 42 is used. With the improvement of the model, the GAH is expected to better guide in identifying the subpopulation of older patients with hematological diseases at risk of toxicity and most suited to benefit from treatment. Although populations used to develop the scoring system of the GAH scale were heterogeneous, the results presented here support its potential usefulness when applied to populations with MDS/AML and CLL, where no validated tools covering geriatric domains are available. In CLL, the Cumulative Illness Rating Scale (CIRS) score discriminate patients suitable for standard treatment [19], but it is limited to measuring the burden of general medical comorbidities.

The GAH scale is based on the number of drugs taken (<5, ≥5, score 0 or 1), gait speed (≥0.8 m/s, <0.8 m/s, score 0 or 1), ADL score (no dependence, any dependence, score 0 or 1), comorbidities (<3, ≥3, score 0 or 1), nutrition (>8, ≤8, on MNA®-SF, score 0 or 1), mental status (<3, ≥3 errors on SPMSQ, score 0 or 1), mood (felt depressed ≤2 days or 3–7 days on CES—D, score 0 or 1), and subjective health status (good, very good, or excellent or poor and fair, score 0 and 1). In this study, it was found to predict toxicity in 66% of patients with a mean age of 78 years. The coefficients for gait speed, ADLs, and nutrition were the only ones that achieved statistical significance. Because the sample size was small and not homogeneous, we decided to keep the eight domains in the model and let future studies with larger sample sizes determine whether it is appropriate to exclude any of the domains.

The GAH scale covers all essential domains recommended for a geriatric assessment in older patients with cancer [4,20]: functional status, comorbidity, falls, depression, cognition, and nutrition. These results add to the literature and show that the GAH scale can be added to the valuable tools that, in the near future, will be applied in clinical care for a more objective assessment to help guide treatment. Due to the retrospective design of this study, treatment was not modified according to the GAH score; a next step would be to address whether the risk of toxicity determined by the GAH score results in changes in treatment decisions and whether such treatment adaptions improve outcomes.

Table 4
Univariate and multivariate regression models evaluating risk factors for developing treatment-related toxicity.

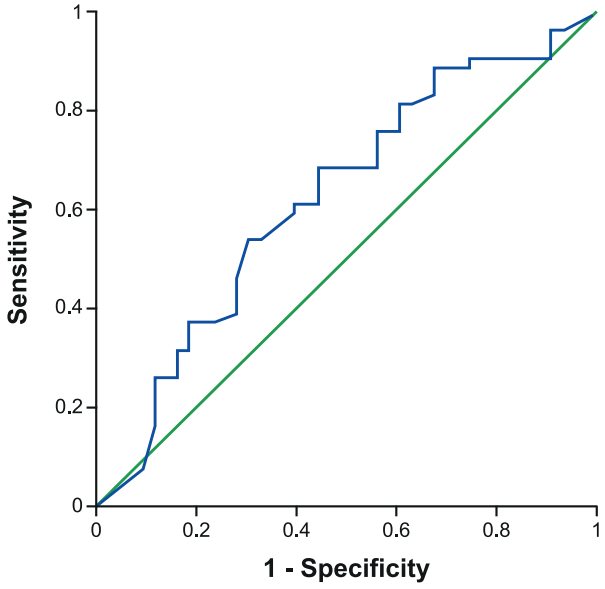
	Univariate analysis		Multivariate analysis	
Variable	Unstandardized coefficient B (95% CI)	P	Unstandardized coefficient B (95% CI)	P
No. of drugs (<5* vs ≥ 5)	56.25 (44.10–68.39)	<0.001	1.15 (−8.96–11.27)	0.821
Gait speed (m/s) (≥0.8* vs <0.8)	52.11 (43.39–60.83)	<0.001	12.29 (3.42–21.15)	**0.007**
Mood (felt depressed ≤2 days* vs 3–7 days) on CES-D	62.06 (44.72–79.41)	<0.001	3.08 (−7.77–13.95)	0.573
ADL (no dependence* vs any dependence)	66.66 (54.06–79.27)	<0.001	21.71 (10.9232.51)	**<0.001**
Subjective health status (good/ very good/ excellent* vs poor and fair) on VES-13	62.79 (50.63–74.94)	<0.001	5.01 (−5.80–15.83)	0.360
Nutrition (>8* vs ≤8) on MNA-SF	64.40 (56.96–71.84)	<0.001	39.71 (30.95–48.47)	**<0.001**
Mental Status* (<3, ≥3 errors) on SPMSQ	55.00 (31.73–78.26)	<0.001	1.14 (−10.21–12.51)	0.842
Comorbidities (<3* vs ≥3)	55.00 (31.73–78.26)	<0.001	4.03 (−8.04–16.11)	0.508

* Reference category. Abbreviations: ADL, activities of daily living; CES—D, Centre for epidemiological Studies Depression Scale; MNA-SF, Short version of the complete Mini-Nutritional Assessment questionnaire; SPMSQ, Short Portable Mental Status Questionnaire; VES-13, Vulnerable Elders Survey Instrument.

Table 5
Diagnosis accuracy of the GAH scale for treatment-predicting tolerability.

Cut-off ≥	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
3.2	96.3 (87.5–98.98)	9.3 (3.7–21.6)	57.1 (46.3–67.5)	66.7 (22.3–95.7)
41.6	**68.5** (55.3–79.3)	**55.8** (41.1–69.6)	**66.1** (52.2–78.2)	**58.5** (42.1–73.7)
84.6	3.7 (1.0–12.5)	95.3 (84.5–98.7)	50.0 (6.8–93.2)	44.1 (33.8–54.8)

Abbreviations: AUC, area under the curve; NPV negative predictive value; PPV positive predictive value. Data include the 95% confidence interval (CI).



AUC	SE	95% CI	*P*-value
0.625	0.058	0.512 - 0.739	0.035

Fig. 2. ROC-curve for the GAH scale. Figure shows sensitivity and specificity of the cutoff point that predicts treatment toxicity in older patients with hematological diseases. Abbreviations: AUC, area under curve; SE, standard error; CI, confidence interval.

In MM, the IMWG-frailty [10] and R-MCI [13,21] are 'reference' prognostic indexes largely validated in clinical studies and cohorts of newly diagnosed patients who received standard treatment. Although we could not directly compare the GAH scale with these risk models using the same data set, which prevent us from drawing conclusions, the results presented here are promising. The IMWG [10] is based on age (76–80, >80, score 1 or 2), Charlson Comorbidity Index (≥2, score 1), ADL, (≤4, score 1), and IADL (≤5, score 1). The R-MCI [13, 21] is a 9-point weighted score, based on age (60–69, ≥70, score 1 or 2), Karnofsky PS (80–90, ≤70, score 2 or 3), eGFR (<6, score 1), moderate/severe pulmonary disease (score 1), moderate/severe frailty phenotype-based on poor endurance, low physical activity, slow gait speed (score 1), and unfavorable cytogenetics (score 1). Both of them, although tested in populations with a ten-year age difference, classify patients into risk groups (fit, intermediate-fit, and frail) with clearly different survival outcomes. However, the inclusion of organ impairment and chromosomal abnormalities in the R-MCI improved the prediction model in all risk groups and is considered more straightforward than IMWG [21].

Others have defined alternative models in patients with MM. The UK Myeloma Risk Alliance Risk Profile (MRP) [22] is based on age and measurements of function (World Health Organization [WHO] PS), International Staging System (ISS) and C-reactive protein (CRP), while the Medicare Health Outcome Survey (MHOS)-based frailty index, developed by applying the accumulation of deficits approach, was built by combining ADL, chronic health conditions, functioning, general health, and mental health [23]. Both of them appears to be prognostic of OS, and the MRP also of therapy delivery, but data on its utility in predicting treatment-related toxicity and early treatment cessation are still awaited. Other models, based on large studies which are still in validation stages, explore frailty in myeloma based on age, PS, comorbidity, [24] or the N-terminal fragment of the B-type natriuretic peptide (NT-proBNP), [25] which have proven to be good indicators of toxicity and survival. To date, all approaches have mainly focused on survival, while endpoints of treatment discontinuation and toxicity require further investigation.

The evidence base for frailty assessments and their effect on the care of older adults with hematological malignancies has grown significantly over the past two decades. Efforts are underway to develop a clinical prediction model that is less time consuming, based on parameters and features easily available or implemented in current practice, and, most importantly, that provides a frailty score that will inform the physician that a complication with treatment may occur. Using the GAH scale, patients with a total score of ≤42 have a 58% of probability of not developing toxicity (NPV 58.5%), while for those scoring >42, the probability of experiencing toxicity is 66% (PPV 66%). Nonetheless, among patients exhibiting similar GAH scores, different protocols/drugs may cause a wide range of toxicities that undermine predictive role of the scoring system. Therefore, we encourage publications of all present indexes to assist future studies in refining and implementing the most suitable scale depending on the objective.

In the opinion of the experts, none of the prediction models developed in MM are dynamic, that is, none of them 'seem to accommodate changes in disease-related frailty that might be minimised by effective therapy' [22,26]. In this sense, attempts to effectively manage patients who are frail must be focused on minimization of the risk of toxicity as a way to optimize therapy. If a patient is identified as at high risk of toxicity by GAH, treatment adaptions can be made, including non-oncological interventions to enhance his/her condition before starting treatment.

With the exception of the GAH scale, none of the frailty scores mentioned above include nutritional status as a prognostic variable, although this is correlated with tolerability to chemotherapy and survival [27]. Indeed, in the GAH scale, nutritional status is associated with a higher significant weighting coefficient. More recently, preliminary analysis of the HOVON trial [28] showed that aging-associated domains such as gait speed and grip strength differed within IMWG frailty groups, highlighting that both might be complementary in predicting outcomes. Additional cognitive and nutritional geriatric assessments were performed. In fact, a new proposed risk model in MM is being considered focused on aging outcome beyond disease [29]. However, in the prediction model for toxicities in older adults, the hematologic status is probably as important as any frailty score, assuming that hematological toxicities are more driven by bone marrow reserve.

There are some limitations in this study that should be considered when interpreting its findings, including the retrospective design, the limited sample size, and having performed the analysis in quite distinct diseases with different treatments and potential complications. This study also did not describe the treatments administered and whether they were similar for all patients; in addition, given the timing of the study, no patients received treatment with new drugs such as monoclonal antibodies, making this population less reflective of a contemporary cohort. Moreover, the low number of patients with CLL precluded us from making any conclusion in regards to this disorder. The inclusion in the analysis of only patients receiving individualized front-line therapy based on the risk of chemotherapy toxicity rather than on clinical judgement avoids any potential bias in the prediction model.

In summary, this study identifies the GAH cut-off point that best discriminates older patients with hematological malignancy at risk of toxicity. This model is easy to perform in clinical practice and could be used as a valid new standard to predict toxicity in the management of newly diagnosed patients.

To confirm these results, the GAH scale is being prospectively tested in 300 patients diagnosed with AML and MM participating in the QoLMMBuS study with protocol code CEL-MIE-2016-01. However, given the study limitations discussed above, and while future studies in clinical practice improve the model, clinicians should not use the GAH scale in isolation when making treatment decisions to allocate patients to some therapies since the risk of under or over-treatment would still be too high. Future studies are warranted to investigate how the GAH scale

performs in predicting toxicity compared to other available toxicity calculators and whether the scale maintains predictive ability in identifying the risk of toxicity in the new era of cancer therapy.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Hospital Universitario de la Ribera, Alzira (Valencia, Spain). All participants gave written informed consent in accordance with the Declaration of Helsinki. The ethical committee approved a waiver of informed consent for dead participants.

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Authors' contributions

JDLR, AJCJ, AC, DV, and SB conceived and designed the study. All authors acquired data and contributed to the data analysis and interpretation, drafted the manuscript and approved the final version to be published.

Declaration of Competing Interest

EPP declares consulting fees from GSK and AstraZeneca, honoraria for lectures, presentations, speakers bureaus from BMS, Incyte and Sanofi, and support for attending meetings from Janssen, Abbvie and Novartis; CM declares support for attending meetings from Janssen, Abbvie, Novartis, Roche, AstraZeneca and for participating in advisory boards from Janssen; MG declares honoraria for lectures, presentations, speakers bureaus from Celgene, Janssen and Amgen, and for advisory board from Sanofi, Janssen and Amgen; MA declares support for meetings from Novartis and Jazz, and for advisory board from Jazz. CE declares honoraria for lectures, presentations, speakers bureaus from BMS, Sanofi, Janssen, GSK and Amgen, support for meetings from Janssen, BMS, Amgen, Sanofi and GSK, and for participating in advisory boards from Janssen, BMS, Sanofi, GSK. ARP declares honoraria for lectures, presentations, speakers bureaus from Novartis, Janssen, Amgen, BMS, Abbvie and AstraZeneca and for advisory board from BMS, Abbvie, Janssen, Amgen, Sanofi and AstraZeneca. PF, and DV are Celgene employees, and the rest of the authors declare no competing financial conflict outside the submitted work.

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Appendix A. Supplementary data

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