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(Article begins on next page)

Simplified geriatric assessment in older patients with diffuse large B-cell lymphoma: the prospective Elderly Project of the Fondazione Italiana Linfomi.

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Context Summary

Key objective: The Elderly Project is the first prospective study that evaluates the prognostic implications of frailty and comorbidities on the overall survival of older patients with diffuse large B-cell lymphoma (DLBCL).

Knowledge generated:

- We used a large multicentric prospective study of older DLBCL patients to validate a simplified geriatric assessment tool (sGA), which incorporates activities of daily living (ADL), instrumental ADL (IADL), Cumulative Illness Rating Scale for Geriatrics (CIRS-G), and age (\geq or $<$ 80 years)
- The development and validation of the Elderly Prognostic Index (EPI) on an independent series of patients provides clinicians with a unique tool to better account for the complexity of each older DLBCL patient.

Relevance: sGA and EPI are easy-to-use tools that improve prognostic assessment and tailoring treatment objectives of older adults with DLBCL. The clearly identified unmet needs of high-risk older DLBCL patients should be the subject of future investigations.

Abstract

Purpose

To prospectively validate the use of a simplified geriatric assessment (sGA) at diagnosis and to integrate it into a prognostic score for older patients with diffuse large B-cell lymphoma (DLBCL).

Patients and Methods

We conducted the prospective Elderly Project study on patients with DLBCL over age 64 years who underwent our Fondazione Italiana Linfomi (FIL) original GA (oGA) (age, Cumulative Illness Rating Scale for Geriatrics, Activities of Daily Living (ADL), and Instrumental ADL before treatment (NCT02364050). Treatment choice was left to the physician's discretion. The primary endpoint was overall survival (OS).

Results

We analyzed 1163 patients (median age 76 years); 3-yrs OS 65% (95% CI 62-68). Because at multivariate analysis on oGA, age > 80 year retained an independent correlation with OS, we also developed a new, simplified version of the GA (sGA), which classifies patients as fit (55%), unfit (28%) and frail (18%) with significantly different 3-year OS: 75%, 58% and 43% respectively. The sGA groups, International Prognostic Index, and hemoglobin levels were independent predictors of OS and were used to build the Elderly Prognostic Index (EPI). Three risk groups were identified: low (23%), intermediate (48%), and high (29%), with an estimated 3-year OS of 87% (95% CI 81-91), 69% (95% CI 63-73), and 42% (95% CI 36-49), respectively. The EPI was validated using an independent external series of 328 cases.

Conclusion

The Elderly Project validates sGA as an objective tool to assess fitness status and defines the new EPI to predict OS of older DLBCL patients.

Introduction:

Diffuse large B-cell lymphoma (DLBCL) is the most frequent lymphoma subtype; approximately 70% of patients are older than 65 years, and outcomes have significantly improved since rituximab was added to anthracycline-containing regimens.^{1,2} However, the outcome of these patients remains poor compared to that of young patients; age-associated conditions significantly contribute to reducing access to therapeutic options and to increasing treatment side effects. Difficulties in the choice of treatment are further increased because older patients are underrepresented in clinical trials,³ and the treatment decision is left to the subjective assessment of the treating physician. In the last few years, integrating geriatric assessment (GA) in the initial evaluation of older patients has emerged as an important tool for identifying multiple geriatric impairments. GA encompasses multiple domains focusing on health issues that may affect treatment tolerance and prognosis and seems more appropriate than age or performance status to define treatment goals and to tailor treatment intensity.^{4,5} Different approaches to GA have been suggested, ranging from a full commitment of geriatricians to the use of single hyper-simplified items for self-assessment.⁶

The Fondazione Italiana Linfomi (FIL) has adopted his original geriatric assessment (oGA) based on a model originally proposed by Balducci⁷ that identifies three categories (fit, unfit, and frail) according to age, Activities of Daily Living (ADL),⁸ Instrumental Activities of Daily Living (IADL),⁹ and the Cumulative Illness Rating Scale for Geriatrics (CIRS-G).¹⁰ A pivotal observational prospective study conducted by FIL on 173 patients with DLBCL over age 70 years suggested a correlation between oGA scores and patient survival.¹¹ This study also confirmed that oGA was feasible in the multicentric setting and could be administered by the referring oncologist-hematologist. On the basis of these results, FIL designed a broader observational study, the Elderly Project, with the aim of further validating and improving the oGA and of assessing the added prognostic value of administering a simplified geriatric assessment (sGA) in older DLBCL patients.

Methods

The Elderly Project is a prospective multicenter observational study. The main purpose was to evaluate the impact of sGA on overall survival in a large cohort of older patients with newly diagnosed DLBCL. The study was conducted in three main steps: (i) validation of oGA on the collected prospective patients; (ii) refinement of a new sGA to better account for possible confounding factors, and (iii) develop and validate a prognostic model that integrates patient- and lymphoma-related features.

The study was conducted among 36 of the Italian oncology-hematology centers of the FIL and was approved by the ethics committee at each participating institution; data collection was performed using a web-based eCRF (Openclinica TM).

The prospective registry included all consecutive patients with histologic confirmation of DLBCL, age ≥ 65 years, signed informed consent, and with oGA results available. Patients with a diagnosis other than DLBCL, including follicular lymphoma grade 3b or high-grade lymphoma, were excluded. The new sGA was performed using age (\geq or < 80 years) and CIRS-G¹⁰, ADL,⁸ and IADL scores.⁹ Each patient was classified as fit, unfit, or frail according to the sGA criteria (table 1) and by using a web-based calculator.

In addition to demographics and sCGA, standard clinical and laboratory parameters, treatment choice, and details on patient outcome were also collected. Chemotherapy regimens were classified comparing the actual delivered anthracycline dose with the theoretical dose calculated for each patient for the whole treatment program. Treatments were grouped as either full dose (FD; from 70 to 100% of theoretical dose) or reduced dose (RD; less than 70% of full dose);¹² regimens that did not include anthracyclines were grouped together in a third group of “palliative” therapies (PT). Patient survival had to be updated at least once a year since registration. Data included patient’s status at last follow-up, relapse/progression details, and death with its main cause. Causes of deaths were grouped into lymphoma-related, treatment-related, and others based on local assessment. The protocol did not

include any recommendation for patient management, which was left to the treating physician's discretion and did not have to be based on sGA results. The main study endpoint was OS, defined as the time from the date of diagnosis to the date of death from any cause or last clinical contact.

Statistics

The OS was calculated and plotted using Kaplan-Meier estimators, with 95% confidence interval (95% CI). The effect of covariates with 95% CI was estimated using Cox proportional hazard (PH) regression.¹³ The prognostic properties of the final model were verified by means of internal and external validation.

Details about statistical methods are reported in the appendix.

Results

Thirty-six FIL centers registered 1353 patients in the Elderly Project between December 2013 to December 2017; 1207 of these patients were confirmed eligible (appendix figure 1).

The median age was 76 years (65-94).

As reported in the appendix (section Model building), we defined a new sGA starting from the original version to better account for the independent prognostic role of age and fitness status we found in multivariable analysis. Patients were classified as fit, unfit, or frail: 652 (54%), 334 (28%), and 221 (18%), respectively (table 2). Treatment and follow-up details were available for 1163 patients: 737 (63%), 276 (24%), and 150 (13%) received FD, RD, or PT, respectively. The FD was administered to 86%, 48%, and 16% of fit, unfit, and frail patients, respectively (appendix table 1).

The median follow-up of the 1163 patients was 30 months (range 1 to 59 months), and 354 deaths were reported. The causes of death included lymphoma progression (243; 68.6%), treatment-related toxicity (74; 20.9%), second cancer (10; 2.8%), and unknown causes (27; 7.6%). The 3-year OS was 65% (95% CI 62% to 68%). According to sGA scores, the OS was significantly different in the three geriatric

fitness status groups, with HR unfit *vs* fit 1.98 (95% CI 1.55 to 2.54, $P < 0.001$), frail *vs* fit 3.27 (95% CI 2.52 to 4.22, $P < 0.001$) and frail *vs* unfit 1.65 (95% CI 1.26 to 2.14, $P < 0.001$) (figure 1).

The sGA groups, the International Prognostic Index (IPI), and the hemoglobin level were considered as the most important prognostic factors to build the Elderly Prognostic Index (EPI) with a multivariable Cox PH regression model (the building of the model is reported in appendix and the assessment of its adequacy is reported in appendix table 2).

Because 98 patients had incomplete data for the IPI, the model was developed on a cohort of 1065 patients (3-year OS 66%, 95% CI 62% to 69%), and the Cox PH model was internally validated, showing no overfitting (slope shrinkage 0.971) and a good calibration at 36 months of follow-up after 250 bootstrap resamples (appendix table 5 and appendix figure 2A).

The prognostic score was obtained giving a weight to each variable according to its relative importance, derived from the z-Wald values found in the Cox PH model (table 3A). The ratio between the z-score for any factor was divided by minimum z-score observed (IPI 2, considered as reference). Finally, the weights were obtained rounding the ratio, and the score was the sum of weights. We thus obtained a score ranging from 0 to 8 that showed a good correlation with OS (appendix figure 3). Patients were grouped into three main risk groups: low (score 0-1, 23% of patients), intermediate (score 2-5, 48% of patients), and high (score 6-8, 29% of patients). The three risk groups showed an estimated 3-year OS of 87% (95% CI 81% to 91%), 69% (95% CI 63% to 73%), and 42% (95% CI 36% to 49%), respectively (figure 2A and table 3B).

The HR between the intermediate *vs* low risk was 2.57, 95% CI 1.72 to 3.84 ($P < 0.001$) and between high *vs* intermediate risk it was 2.41, 95% CI 1.91 to 3.05 ($P < 0.001$) (table 3B).

A sensitivity analysis was also conducted to assess the EPI model (details provided in the appendix).

Full dose therapy was prescribed in 89%, 70%, and 37% of patients classified as low risk, intermediate risk, or high risk, respectively; RD was prescribed in 10%, 24%, and 35%, respectively, and PT in <1%, 7%, and 28%, respectively. Overall survival according to the EPI risk groups and type of therapy is shown in appendix figure 4. Differences in OS among EPI groups were confirmed when the analysis was limited only to patients treated with anthracyclines (FD + RD) (appendix figure 5).

Finally, the prognostic role of the EPI model was also validated for progression-free survival (PFS) and disease-free survival (DFS) (appendix figure 6).

External validation

We collected a total of 456 cases for external validation from Italy (172),¹¹ Australia (204),¹⁴ and Brazil (80). The median follow-up was 30 months (range 1-56 months).

Complete data for sGA, IPI, and hemoglobin level were available for 328 (78%) cases. One hundred and seventeen deaths were reported (69% were due to lymphoma progression); the 3-year OS was 61% (95% CI 55% to 67%). Applying the EPI to the validation dataset, patients were classified into three risk groups as follows (0-1, low risk: n=73, 22%; 2-5, intermediate risk: n=150, 46%; 6-8, high risk: n=105, 32%) (table 4). The 3-year OS for low, intermediate, and high risk were 85% (95% CI 71% to 93%), 65% (95% CI 55% to 73%), and 44% (95% CI 34% to 54%), respectively. The HR between the intermediate and low risk was 2.14 (95% CI 1.08 to 4.24, $P=0.029$) and between high vs intermediate risk was 2.18 (95% CI 1.49 to 3.21, $P<0.001$) (table 4 and figure 2B).

The C-index of linear prediction from the Cox PH model in the validation set was 0.684 (CI 95% 0.635 to 0.733) compared with 0.682 (95% CI 0.653 to 0.712) of the training set. The model showed an acceptable external validation of baseline hazard (intercept) and in the discrimination power (slope), considering 18, 24, and 36 months of follow-up (intercept=0 with slope constrained =1, $P=0.302$; slope=0.941 with estimated intercept $P=0.724$ and joint test for intercept =0 and slope =1, $P=0.364$)

(appendix table 5). Also, the model showed an appreciable calibration at 36 months of follow-up (appendix figure 2B).

Discussion

In this study we provide new data to support the use of a simplified geriatric assessment for the initial evaluation of older patients with DLBCL and to better manage the challenging complexity they present. This result was achieved through a refinement of our original GA and by a formal validation of the new sGA obtained as an independent prognostic factor for OS in the large Elderly Project prospective study. In 2009, Tucci demonstrated on a small series of patients that a geriatric assessment is more effective than clinical judgment in identifying older DLBCL patients who might benefit from standard therapy.¹⁵ Since this study, and also based on data from solid tumors, international guidelines^{6,16,17} have increasingly recommended the use of geriatric assessment, but few studies have been conducted on patients with DLBCL. These few studies were mostly based on small or retrospective series, and none was available to identify a standardized reproducible tool.¹⁸⁻²⁰

In 2012, two phase II studies of 100 and 91 patients,^{21,22} respectively, modulated therapy based on the geriatric assessment at diagnosis, demonstrating that chemoimmunotherapy adjustments tailored to GA score were associated with manageable toxicity and excellent outcome.

FIL has been using the same oGA in its studies on older patients with DLBCL for several years. In its first experience, 334 older DLBCL patients underwent oGA assessment to identify 224 fit subjects, who were included in a randomized trial between R-CHOP and R-miniCEOP.²³ The remaining 99 frail patients were treated according to the physician's discretion and showed a poorer 5-year OS (28%) compared with fit patients (62%).²⁴

In 2015, FIL performed a pivotal prospective study with oGA, enrolling 173 patients with DLBCL (fit 46%, unfit 16%, frail 38%) treated with curative or palliative intent based on clinical judgement.¹¹ Fit patients showed better 2-year OS than non-fit patients (84% vs 47%; $P < 0.0001$). Due to the small size

of that study population, we were not able to assess the added value of having an intermediate group of unfit patients.

More recently, Ong et al.¹⁴ retrospectively evaluated 205 patients with newly diagnosed DLBCL using the same oGA tool adopted in our study to explore its utility in predicting treatment toxicity. Three-year OS of fit patients (82%) was superior to that of frail patients (53%) but not statistically different from unfit patients (60%). Again, this was likely due to the small sample size.

Our validation of this new sGA to predict OS of older patients with DLBCL adds a significant contribution to the integration of geriatric assessment in the initial evaluation of these patients. Thanks to the large study population of the Elderly Project, we were able to definitively show the existence of an intermediate group of unfit patients, thereby improving the previously adopted two-group model. We simplified our original GA by using age slightly differently in the definition of fitness status as reported in table 1.

Unlike a full geriatric assessment, our simplified model can be administered by the oncologist-hematologist during a regularly scheduled appointment; it takes less than 10 minutes and either a paper- or web-based calculator can be used, as we did in our project, which reduced the time needed even more. Other groups are currently working on the same line of research but with a different point of view as they are using screening tools to identify fit patients who do not require a full geriatric consultation.²⁵⁻²⁷ This approach is reasonable as it quickly identifies the majority of patients who do not need any additional assessment. We propose our sGA as a useful tool for clinicians that identifies and objectively measures main inabilities and comorbidities, providing a more complete yet simplified initial assessment. Of note, sGA does not substitute a formal geriatric consultation, which should always be done when appropriate. Moreover, sGA cannot be considered as a complete tool for the evaluation of older subjects as some dimensions are not included (i.e. socioeconomic status, social functioning, caregiver, etc.).

In light of the interaction between age and sGA, we were able to define novel prognostic age groups that added independent details to other patient and disease features, making it possible to predict individual risk and prompting the definition of an integrated prognostic model. Adopting an age cutoff of 80 years might raise some criticism. This cutoff, however, has traditionally been used as one of the inclusion criteria in the pivotal R-CHOP studies^{1,2}, and identifies a group of patients unlikely to tolerate a standard immunochemotherapy regimen.^{28,29} Moreover, looking at our dataset, we observed that the management of patients over age 80 frequently changed due to therapeutic uncertainties.

We used the same dataset as the sGA validation to build the Elderly Prognostic Index. Based on the Elderly Prognostic Index, 23% of patients are classified at low risk, and their excellent projected 3-year OS of 87% makes this group of patients suitable for curative approaches similar to those adopted for those below age 60 years. These patients must be younger than age 80 and have a low-risk lymphoma with no or mild impairment in ADL, IADL, and CIRS as defined by the sGA score. In the intermediate-risk group, which accounts for approximately half of older DLBCL patients, the individual risk is the result of a more complex interaction between patient status and the disease. Nonetheless, the projected 3-year OS of 69% identifies curing lymphoma as the main goal of therapy. Looking at prescribed therapies, however, one out of four patients at intermediate risk is treated with reduced-dose regimens, without any significant difference in overall survival compared to full dose. Thus, full dose therapy seems a reasonable option also for this intermediate group of patients but reduced-dose therapies should be considered a good alternative.

Finally, 29% of subjects have a high-risk profile, which is associated with dismal survival rates. These patients combine both an impairment of fitness status and high-risk lymphoma features. The high heterogeneity of prescribed therapies and the highest frequency of palliative therapy use (29%) in this group confirms the lack of consensus about patient management and about treatment objectives. To

confirm its strength, we validated the EPI on an independent series of older patients with DLBCL from three different datasets.

Despite the high number of our cases and the solidity of the results shown, we are aware that our study has some limitations. Ninety-eight patients were excluded from the model definition due to missing IPI values (mainly LDH and details on extranodal sites). Although missing data could have had some effect on model definition, this rate of 8.4% is expected for an unselected population of older patients. Treatment choice was left to the physician's discretion and may have had a significant effect on survival. Details on treatment reductions, which can contribute to the success of therapy, are sometimes incomplete, or even lacking altogether. However, this paper reflects a real-life setting.

In conclusion, the Elderly Project definitively confirms the importance of performing a geriatric assessment before starting treatment in older patients with DLBCL. The sGA adopted in our study is an objective, reproducible tool that can be easily managed by the oncologist-hematologist. The time has come to consider the fitness status of older DLBCL patients to better identify their treatment goals. The EPI is the first prognostic index to integrate fitness evaluation into prognosis in older DLBCL patients, which contributes to improving patient assessment. EPI clearly identifies for the first time a high-risk group of older DLBCL patients that has associated with clear unmet needs and that should be the subject of future investigations.

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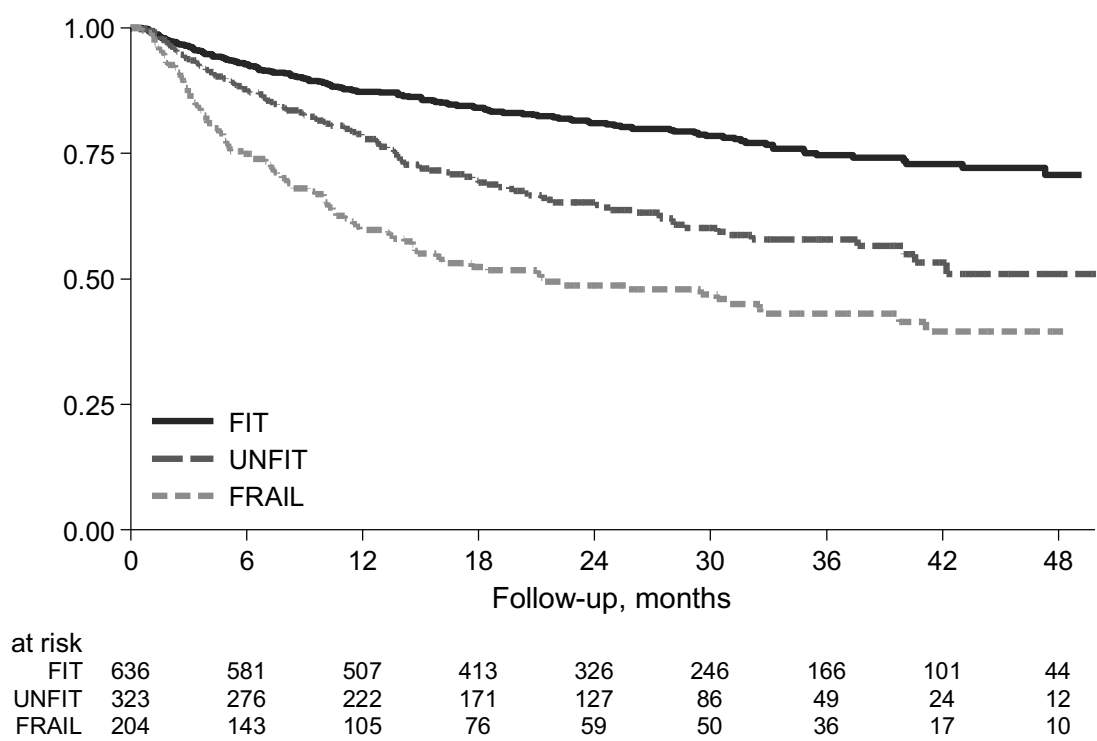
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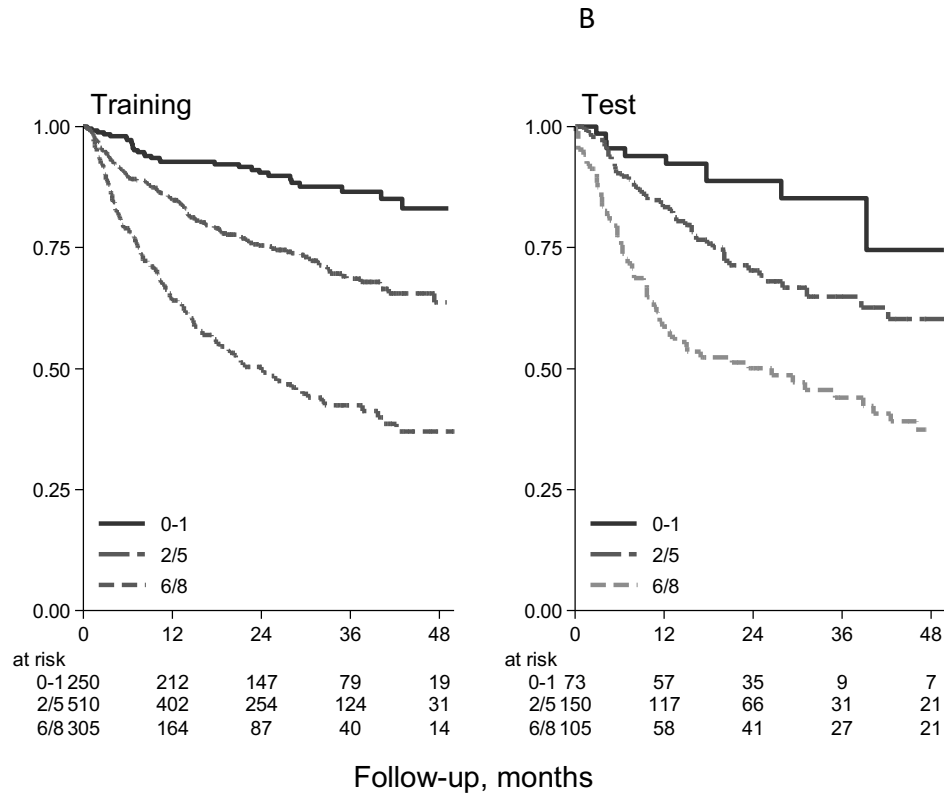
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Figure 1. Overall survival by sGA in all patients with treatment details available (N=1163).



sGA: simplified Geriatric Assessment

Figure 2: Overall survival stratified by EPI in the training (A: 1065 patients) and in the validation (B: 328 patients) samples.



EPI: Elderly Prognostic Index

Table 1. Criteria for sGA assessment

	FIT	UNFIT		FRAIL
ADL	$\geq 5^*$	$< 5^*$	6^*	$< 6^*$
IADL	$\geq 6^*$	$< 6^*$	8^*	$< 8^*$
CIRS-G	0 score =3-4, ≤ 8 score =2	1 score =3-4, > 8 score =2	0 score =3-4, < 5 score =2	1 score =3-4, ≥ 5 score =2
Age	< 80	< 80	≥ 80	≥ 80

* number of residual functions

sGA: simplified Geriatric Assessment; ADL: Activity of Daily Living; IADL: Instrumental ADL; CIRS-G: Cumulative Illness Rating Scale for Geriatrics

Table 2. Baseline characteristics of DLBCL patients included in the Elderly Project (n=1207).

Variable		sGA, n (%)			Total n (%)	P value
		FIT n = 652	UNFIT n = 334	FRAIL n = 221		
Age, median (range)	years	72 (65 to 79)	80 (65 to 94)	84 (80 to 94)	76 (65 to 94)	<0.001
Age	>80	-	168 (50)	221 (100)	389 (32)	<0.001
Sex	Male	343 (53)	172 (51)	94 (43)	609 (50)	0.032
Stage	III-IV	427 (66)	236 (71)	148 (68)	811 (67)	0.217
MV		3	3	3	9	
Extranodal sites	>1	187 (29)	91 (28)	58 (27)	336 (29)	0.795
MV		17	13	7	37	
ECOG-PS	>1	71 (11)	84 (25)	85 (39)	240 (20)	<0.001
MV		1	2	1	4	
LDH	>ULN	330 (53)	184 (59)	109 (56)	632 (55)	0.180
MV		27	23	25	75	
IPI	3-5	312 (51)	180 (60)	120 (62)	612 (56)	0.004
MV		42	34	29	105	
Symptoms	B	159 (24)	96 (29)	60 (27)	315 (26)	0.303
MV		-	-	2	2	
Hb, median (range)	g/dL	12.7 (6.2 to 17.5)	12.2 (5.8 to 16.5)	11.7 (6.2 to 16.5)	12.3 (5.8 to 17.5)	<0.001
Hemoglobin	<12 g/dL	234 (37)	146 (45)	115 (56)	495 (42)	<0.001
MV		16	11	14	41	
Albumin	<3.5 g/dL	131 (30)	64 (32)	62 (50)	257 (34)	<0.001
MV		217	137	98	452	

Percentages referred on cases. Excluding those with missing values

p-value: chi2 test of Fisher's exact test.

NOTE. Because of rounding, percentages may not total 100

sGA: simplified Geriatric Assessment; MV: missing values; LDH: lactate dehydrogenase; ULN: upper limit of normal; IPI: International Prognostic Index; Hb: hemoglobin; ECOG-PS: Performance Status.

Table 3. Multivariable Cox PH regression with internal validation parameters (A) and EPI model definition (B) (n=1065).

(A)					
Factors	HR (95% CI)	z-score	Ratio*	Weight	P value
FIT	1.00	-	-		-
UNFIT	1.93 (1.49 to 2.50)	4.97	2.59	3	<0.001
FRAIL	2.74 (2.07 to 3.62)	7.09	3.69	4	<0.001
IPI 1	1.00				-
IPI 2	1.55 (0.99 to 2.44)	1.92	1.00	1	0.055
IPI 3-5	2.90 (1.93 to 4.35)	5.14	2.68	3	<0.001
Hb <12 g/dL	1.28 (1.02 to 1.60)	2.13	1.11	1	0.033
(B)					
EPI model	N (%)	3-yr OS (95%CI)	HR (95%CI)	P value	
Risk groups (Score)	1065	66 (62 to 69)	-	-	
Low (0-1)	250 (23)	87 (81 to 91)	1.00	-	
Intermediate (2-5)	510 (48)	69 (63 to 73)	2.57 (1.72 to 3.84)	<0001	
High (6-8)	305 (29)	42 (36 to 49)	6.21 (4.17 to 9.25)	<0.001	
High vs Intermediate	-		2.41 (1.91 to 3.05)	<0.001	

* Ratio: ratio between the z-score for any factor divided by minimum z-score observed (IPI 2, considered as reference).

The weights were obtained rounding the ratio. Score: sum of weights.

Internal validation performed after 250 bootstrap resamples

HR: Hazard ratio; CI: Confidence interval; EPI: Elderly Prognostic Index; OS: Overall survival

Table 4. Baseline characteristics of patients in the training and in the validation samples, and external validation of the EPI.

Variable		Training	External validation	P value
		n = 1065	n = 328	
Age, years	Median (range)	75 (65 to 94)	75 (65 to 99)	0.971
Age, years	>80	325 (31)	88 (27)	0.214
Hemoglobin, g/dL	Median (range)	12.3 (5.8 to 17.5)	12.2 (5.8 to 17.1)	0.890
Hemoglobin, g/dL	<12 g/dL	450 (42)	129 (39)	0.370
sGA				0.003
	FIT	596 (56)	148 (465)	
	UNFIT	291 (27)	112 (34)	
	FRAIL	178 (17)	68 (21)	
IPI				0.011
	0-1	194 (18)	85 (26)	
	2	287 (27)	83 (25)	
	3-5	584 (55)	160 (49)	
3-year OS % (95% CI)		66 (62 to 69)	61 (55 to 67)	0.084
EPI Risk groups (External validation)		N (%)	3-yr OS% (95% CI)	HR (95% CI)
Low (0-1)		73 (22)	85 (71 to 93)	1.00
Intermediate (2-5)		150 (46)	65 (55 to 73)	2.14 (1.08 to 4.24)
				P 0.029
High (6-8)		105 (32)	44 (34 to 54)	4.68 (2.39 to 9.14)
				P <0.001
High vs Intermediate		-	-	2.18 (1.49 to 3.21)
				P <0.001

NOTE. Because of rounding, percentages may not total 100

sGA: simplified Geriatric Assessment; IPI: International Prognostic Index; OS: Overall Survival; HR: Hazard ratio

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