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Life expectancy of young adults with follicular lymphoma

A. Conconi[1,†], C. Lobetti-Bodoni[2,†‡], S. Montoto[3], A. Lopez-Guillermo[4], R. Coutinho[4], J. Matthews[3], S. Franceschetti[5], F. Bertoni[2,6], A. Moccia[2], P. M. V. Rancoita[6,7], J. Gribben[3], F. Cavalli[2], G. Gaidano[5], T. A. Lister[3], E. Montserrat[4], M. Ghielmini[2] & E. Zucca[2*]

[1]Unit of Hematology, Department of Internal Medicine, Ospedale degli Infermi, Biella, Italy; [2]Oncology Institute of Southern Switzerland (IOSI), Ospedale San Giovanni, Bellinzona, Switzerland; [3]Barts Cancer Institute, Queen Mary University of London, London, UK; [4]Institute of Hematology and Oncology, Hospital Clínic, IDIBAPS, University of Barcelona, Barcelona, Spain; [5]Division of Hematology, Department of Translational Medicine, Amedeo Avogadro University of Eastern Piedmont and AOU Maggiore della Carità, Novara, Italy; [6]Lymphoma and Genomics Research Program, Institute of Oncology Research (IOR), Bellinzona; [7]Dalle Molle Institute for Artificial Intelligence (IDSIA), Manno-Lugano, Switzerland

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Background: This study was aimed at investigating the clinical features and outcomes of follicular lymphoma (FL) patients younger than 40 years, which have not been extensively investigated yet.

Patients and methods: One hundred and fifty-five patients younger than 40 years were retrospectively studied from a series of 1002 FL patients diagnosed in four different European Oncology Centres (Barcelona, Spain; Bellinzona, Switzerland; London, UK; Novara, Italy) from 1985 to 2010.

Results: Patients younger than 40 had a lower incidence of elevated LDH, high beta2-microglobulin, and a high-risk Follicular Lymphoma International Prognostic Index (FLIPI) score, whereas bone marrow involvement and bulky and disseminated lymphadenopathy were more frequent. At a median follow-up of 10 years, younger patients, in comparison with those older than 40, had significantly better overall (OS), cause-specific survival (CSS), and progression-free survival (PFS), with 10-year OS rate of 81% versus 51% ($P < 0.0001$), 10-year CSS rate of 82% versus 60% ($P < 0.0001$), and 10-year PFS of 39% versus 24% ($P = 0.0098$). However, there were no significant CSS and PFS differences in comparison with the patients aged 40–60. In multivariate analysis, having the lymphoma diagnosed in the last two decades and a favourable FLIPI score were associated with a significantly longer PFS and CSS in younger patients, whereas only FLIPI retained statistical significance for OS.

*Correspondence to: Dr Emanuele Zucca, Oncology Institute of Southern Switzerland (IOSI), Ospedale San Giovanni, 6500 Bellinzona, Switzerland. Tel: +41-91-811-90-40; Fax: +41-91-811-91-82; E-mail: emanuele.zucca@eoc.ch

†Both authors have equally contributed.
‡Present address: Department of Clinical Haematology, Royal Manchester Infirmary Hospital, Manchester, UK.

Conclusions: In our series, FL patients younger than 40 have a median OS of 24 years and their outcome seems to be improving over time. However, they still have a significantly shorter life expectancy than that of an age-matched general healthy population.

Key words: follicular lymphoma, age, life expectancy, young adults, prognosis, survival

introduction

Follicular lymphoma (FL) typically displays an indolent clinical course [1–5]. Most patients present with disseminated disease, nearly all relapse after response to initial therapy, and a proportion experience histological transformation into aggressive entities [1–5]. Improvement in patient survival has been reported during the last decades [6–13], mainly due to the addition of rituximab to the treatment options, but also to a better supportive care.

Approximately half of patients with FL are diagnosed after the age of 60 years. However, a sizeable proportion of patients are diagnosed before 40 years: in this context, the diagnosis of FL could strongly impact on quality and expectancy of life. However, the clinical features and outcomes of younger adult patients with FL have not been extensively investigated yet.

The purpose of the present study was to compare, in a large series of consecutive FL cases diagnosed in the last 25 years in four European Centres, the clinicopathological characteristics of patients diagnosed before 40 years of age with those of an older population.

patients and methods

The clinical information from adult patients diagnosed with FL between 1985 and 2010 in four European Oncology Institutions (Barcelona, Spain, $n = 366$; Bellinzona, Switzerland, $n = 255$; London, UK, $n = 273$; Novara, Italy, $n = 108$) were collected and merged into a single database. The final database gathered information regarding main demographic (age, gender, and date of diagnosis) and clinicopathological features [histological grade, nodal and extranodal involved sites, Ann Arbor stage, Eastern Cooperative Oncology Group performance status, B symptoms, serum lactate dehydrogenase (LDH), serum beta2-microglobulin (β2MG), erythrocyte sedimentation rate (ESR), and bulky disease (defined as >7 cm)], as well as the type of first-line treatment, relapse pattern, and outcome (duration of survival and cause of death). The FL International Prognostic Index (FLIPI) [14] was calculated, whenever possible, using the recorded information.

Overall survival (OS), cause-specific survival (CSS), and progression-free survival (PFS) were defined according to the revised response criteria for malignant lymphoma [15]. Follow-up was calculated as the median time to censoring using a reverse Kaplan–Meier analysis [16]. Survival probabilities were calculated using the life-table method, and survival curves were estimated by the Kaplan–Meier method with upper and lower confidence bands calculated using Greenwood's approximation; differences between curves were analysed using the log-rank test (with the trend test as appropriate). The Cox proportional hazard model was used for uni- and multivariate analyses and estimation of relative risk and its confidence interval (CI). Binomial exact 95% CIs were calculated for incidence percentages. Either the χ^2 test or Fisher's exact test was used for testing associations in two-way tables, as appropriate; P-values of 0.05 or less (two-sided test) were considered to indicate statistical difference. Statistical analysis was conducted using the STATA Release 11 statistical software package (StataCorp 2009, College Station, TX).

results

patient population

Data were available for 1002 FL patients. Median age at diagnosis was 56 (range, 21–91) years. One hundred and fifty-two (15%) patients were younger than 40 years at the time of diagnosis.

A comparison of clinical features at diagnosis between patients ≤40 and >40 years was carried out using univariate analysis and is reported in Table 1. Patients <40 years had a lower incidence of elevated LDH, high β2MG, and a high-risk FLIPI score, whereas bone marrow involvement, bulky adenopathy (>7 cm), and involvement of more than four nodal lesions were significantly more frequent in this age group.

first-line treatment

Forty-two (28%) of the patients younger than 40 and 299 (35%) of the older were asymptomatic and underwent watchful waiting,

Table 1. Comparison of the main clinicopathological features of follicular lymphoma patients younger and older than 40 years

Feature	Age ≤40 years *n* (%)	Age >40 years *n* (%)	*P*-value
Male sex	72 (47)	380 (45)	0.543
ECOG PS >1 ($n = 700$)	7 (6)	66 (11)	0.096
B symptoms ($n = 861$)	26 (18)	109 (15)	0.414
BM involvement	83 (55)	336 (40)	0.001
Era of diagnosis			
<1990	27 (18)	106 (12)	0.011
1990–2000	68 (45)	316 (37)	
>2000	57 (38)	428 (50)	
Stage ($n = 920$)			
I–II	33 (22)	216 (28)	0.140
III–IV	116 (78)	555 (72)	
Nodal sites >4 ($n = 791$)	56 (43)	163 (25)	<0.0001
LDH > ULN ($n = 834$)	18 (14)	160 (23)	<0.026
Hb <12 g/dl ($n = 872$)	19 (15)	118 (16)	0.710
FLIPI ($n = 716$)			
Low-risk (0–1)	65 (55)	242 (40)	0.002
Intermediate (2)	33 (28)	166 (28)	
High-risk (3–5)	20 (17)	190 (32)	
β2MG > ULN ($n = 484$)	20 (26)	155 (38)	0.035
ESR >30 mm/h ($n = 588$)	8 (10)	93 (18)	0.067
Bulk >7 cm ($n = 585$)	43(46)	90 (18)	<0.0001
Histological grade ($n = 562$)			
1	45 (54)	226 (47)	0.463
2	31 (37)	184 (38)	
3a	6 (7)	50 (10)	
3b	1 (1)	19 (4)	

ECOG PS, Eastern Cooperative Oncology Group performance status; BM, bone marrow; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; ULN, upper level normal; β2MG, beta2-microglobulin; ESR, erythrocyte sedimentation rate; Hb, haemoglobin.

Table 2. Comparison of first-line treatment type in patients younger and older than 40 years[a]

	Follicular lymphoma any age *n* (%)	Age ≤40 *n* (%)	Age >40 *n* (%)	*P*-value
RT only	72 (8)	14 (10)	58 (7)	0.261
Rituximab	197 (21)	16 (11)	181 (23)	0.003
Alone	33 (4)	3 (2)	30 (4)	
Plus chemotherapy	164 (17)	13 (9)	151 (19)	
Single-alkylating agents[b] or CVP	297 (32)	44 (31)	253 (32)	0.956
Doxorubicin-containing regimen	327 (35)	58 (41)	269 (34)	0.075
Purine analogues[c]-containing regimen	72 (8)	11 (8)	61 (8)	0.927

RT, radiotherapy.
[a]One hundred and thirty-eight patients initially managed expectantly and never given anticancer treatments are not included.
[b]Mainly chlorambucil; CVP, cyclophosphamide, vincristine, and prednisone.
[c]Mainly fludarabine.

defined as deliberate non-intervention for at least 3 months after diagnosis. Overall, 138 patients (10 of whom younger than 40) never received any therapy and 40 of them have died.

Lymphoma treatment, according to protocols used at the time, was eventually given to 862/1000 patients with available data (86%), including 142 patients younger than 40. Treatment was administered immediately to 659 and, when disease became symptomatic, to 203 of the 341 patients initially managed with watchful waiting. Information on the type of front-line therapy was recorded in 939 cases (Table 2). The difference in the frequency of treated patients between those younger than 40 (93%) and those aged 41–60 years (88%) did not reach a statistical significance ($P = 0.053$), but the proportion of the treated was significantly lower (82%) among those older than 60 years ($P = 0.001$).

outcome

The median follow-up was 9.3 years in the overall population, and 10.7 years for the patients younger than 40 at diagnosis. In this latter group, 39 patients have died, 34 of them because of the lymphoma or its treatment toxicity.

The median OS for the whole population was 12.5 years, with a 10-year OS rate of 56% (95% CI 52–60%) and a 20-year OS rate of 33% (95% CI 28–39%). The median CSS was 17 years, with a 10-year CSS rate of 64% (95% CI 60–68%) and a 20-year CSS rate of 47% (95% CI 41–53%). The median PFS was 3.9 years, with a 2-year PFS rate of 67% (95% CI 64–70%), a 5-year PFS of 44% (95% CI 40–47%), and a 10-year PFS of 27% (95% CI 23–30%).

A comparison of survival between different populations according to age (under and over 40 years) was carried out. Younger patients had longer OS, CSS, and PFS. Specifically, 10-year OS was 81% for patients ≤40 years (95% CI 73–87%) versus 51% in the older ones (95% CI 46–55%, $P < 0.0001$); 10-year CSS was 82% for patients ≤40 years (95% CI 74–87%) compared with 60% in the older ones (95% CI 56–64%, $P < 0.0001$; Figure 1). PFS at 2 years was 73% (95% CI 65–79%) for the patients younger than 40 years and 66% (95% CI 63–69%, $P = 0.0098$) for the older, at

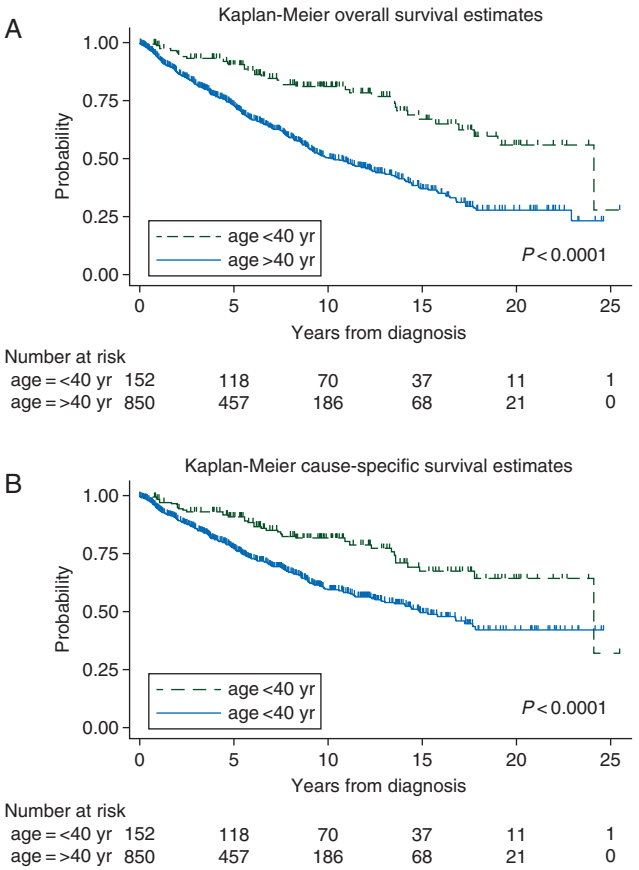

Figure 1. Overall survival (A) and cause specific survival (B) according to age.

5 years was 49% (95% CI 41–57%) for patients younger than 40, and 43% (95% CI 39–46%) for the older ones ($P = 0.0098$). In particular, 2- and 5-year PFS for the patients younger than 40 diagnosed and treated in the last decade were 85% (95% CI 72–92) and 60% (95% CI 45–73), respectively (Figure 2A).

As summarized in Table 3, when further stratifying patients by age groups (≤40, 41–59, and ≥60 years old), those ≤40 years old at diagnosis had longer OS ($P = 0.009$) compared with those 41–59 years old, but no differences were detected in PFS and CSS.

No differences in terms of risk of transformation have been observed (15% of cumulative incidence in both age groups, $P = 0.701$). The cumulative incidence of second tumours was 8% for patients younger than 40 years old, and 11% for the older ones ($P = 0.244$).

analysis of prognostic factors

Age ≤40 years, era of diagnosis, presence of B symptoms, high ESR, elevated serum β2MG, all the variables included in the FLIPI model [14], and the FLIPI risk stratification as a whole had a significant impact on OS, CSS, and PFS on univariate analysis in the overall population. On multivariate analysis for OS and CSS, only the FLIPI stratification, era of diagnosis, serum β2MG, and age ≤40 years retained prognostic significance; on multivariate analysis for PFS, the FLIPI stratification, era of diagnosis, serum β2MG, and presence of B symptoms retained prognostic significance (data not shown).

The results from univariate analysis for OS, CSS, and PFS, in the subgroup of patients aged ≤40 years, are summarized in

Table 4. On multivariate analysis applied to the population aged ≤40 years, the features significantly influencing CSS and PFS were the FLIPI risk at diagnosis and era of diagnosis, while only FLIPI retained statistical significance for OS (Tables 5–7).

discussion

Age is a well-known prognostic factor in FL, included in both the FLIPI [14] and FLIPI2 [17] prognostic indices, and

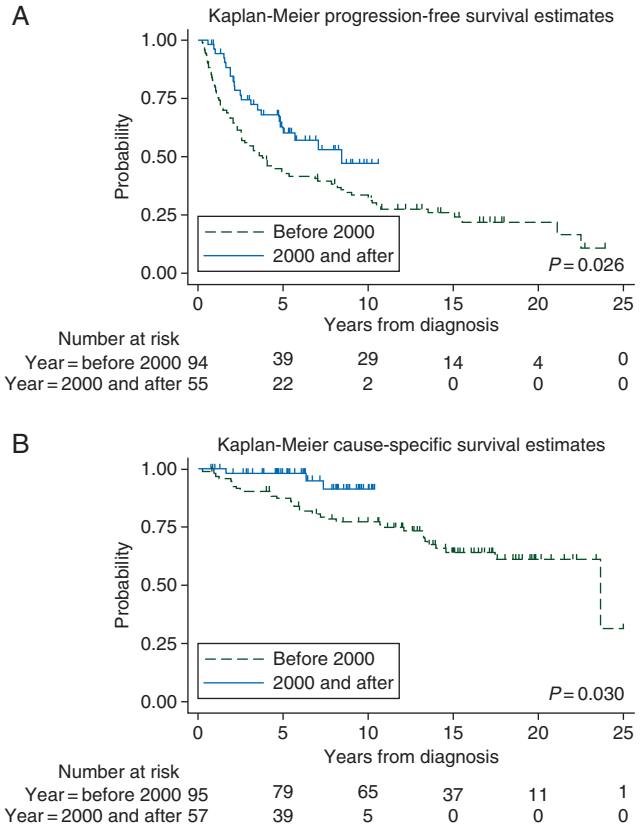

Figure 2. Progression free survival (A) and cause specific survival (B) of patients younger than 40 years according to the year of diagnosis.

presentation before the age of 40 years is relatively rare. Indeed, there are only two published studies specifically addressing the characteristics and outcomes of FL in younger adults [18, 19]. However, these reports were either focused on molecular pathology or conducted entirely in the pre-rituximab era.

In the present series, the patients younger than 40 years represented 15% of all FL cases, and this proportion is higher than those reported from different cancer registries (5%–6% of all FL) [19, 20]. This difference may reflect a different patient selection, being our cases treated at referral tertiary centres.

Due to the retrospective nature of the analysis and the very long period of observation, this study has some limitations. The patients analysed received a large variety of treatment strategies, with less than half of them receiving rituximab as part of front-line therapy, and because of the study length, some parameters were not routinely investigated (e.g. β2MG), resulting in missing data that might have had an impact on the prognostic analysis. Nevertheless, the very large number of patients included in this study allows a reliable description of meaningful clinical features at presentation and disease outcome.

As expected, the survival of patients aged more than 60 years is strongly affected by the competing causes of death, but interestingly the CSS of patients younger than 40 years was similar to that of patients with an age of 41–59 years, suggesting than younger age at diagnosis does not protect from death due to lymphoma. In our series, which did not include subjects younger than 20 years, there were only 9 patients (6%) with age at diagnosis ≤25 years. These younger patients were not assessed for the immunohistochemical and molecular markers of the recently described paediatric FL variant [21, 22]; clinically, they presented a significantly higher frequency of localized disease (55% with stage I–II) in comparison with the rest of the patients younger than 40 years, but other clinical features at diagnosis (performance status, β2MG, and FLIPI score) and outcomes (CSS and OS) were not significantly different (data not shown) from those in patients aged between 25 and 40 years of age. In the last decade, the survival of patients with FL has been steadily improving [6–12]. The year of diagnosis was indeed significantly associated with patients' outcome in our series (supplementary File, available at *Annals of Oncology* online). Figure 2B shows

Table 3. Overall survival, cause-specific survival, and progression-free survival by age groups

A	Overall survival				
Age group	*N* (%)	Median (years)	10-year	20-year	*P*-value
≤40	152 (15)	24	81% (95% CI 73–87%)	56% (95% CI 43–68)	
41–59	426 (43)	16	68% (95% CI 62–73%)	41% (95% CI 32–49%)	≤40 versus 41–59: 0.009
>60	424 (42)	6	32% (95% CI 27–38%)	13% (95% CI7–21%)	≤40 versus >40: <0.0001
B	Cause-specific survival				
Age group	*N* (%)	Median (years)	10-year	20-year	*P*-value
≤40	152 (15)	24	82% (95% CI 74–87%)	65% (95% CI 52–75%)	
41–59	426 (43)	Not reached	74% (95% CI 68–79%)	54% (95% CI 44–63%)	≤40 versus 41–59: 0.152
>60	424 (42)	9	44% (95% CI 37–50%)	28% (95% CI 17–39%)	≤40 versus >40: <0.0001
C	Progression-free survival				
Age group	*N* (%)	Median (years)	2-year	5-year	*P*-value
≤40	151 (15)	4.9	73% (95% CI 65–79%)	49% (95% CI 41–57%)	
41–59	423 (42)	4.5	71% (95% CI 66–75%)	48% (95% CI 42–52%)	≤40 versus 41–59: 0.196
>60	424 (43)	3.3	62% (95% CI 57–66%)	37% (95% CI 32–42%)	≤40 versus >40: 0.0098

Table 4. Univariate analysis for OS, CSS, and PFS in the subgroup of patients aged ≤40 years

Features	OS		CSS		PFS	
	Median (years)	*P*-value	Median (years)	*P*-value	Median (years)	*P*-value
Sex						
Female	19		24		4.7	
Male	NR	0.245	NR	0.318	7	0.311
ECOG PS						
≤1	NR		NR		4.8	
>1	6	<0.0001	6	<0.0001	1.6	0.047
B symptoms						
Absent	24		24		7	
Present	19	0.009	NR	0.013	1.9	0.004
BM involvement						
Absent	NR		NR		10.5	
Present	19	0.077	24	0.088	2.7	0.0009
Era of diagnosis						
<1990	19		24		4.3	
1990–2000	NR		NR		3.6	
>2000	NR	0.079	NR	0.045	8.4	0.020
Stage						
I–II	NR		NR		15	
III–IV	19	0.015	24	0.038	3.7	0.003
Nodal sites						
≤4	NR		NR		10.5	
>4	15	<0.0001	15	0.0006	2.5	<0.0001
LDH						
Normal	NR		NR		7.8	
Elevated	NR	0.002	NR	0.001	1.9	0.174
Haemoglobin (g/dl)						
<12	24		24		7	
≥12	19	0.005	NR	0.012	1.9	0.361
FLIPI						
Low-risk	NR		NR		13.5	
Intermediate	15		15		2.7	
High-risk	19	<0.0001	NR	0.0001	1.9	<0.0001
β2MG						
Normal	NR		NR		10.1	
Elevated	14	0.0006	14	0.0002	2.4	0.003
ESR						
≤30 mm/h	24		24		8.4	
>30 mm/h	NR	0.320	NR	0.320	1.9	0.350
Bulk (cm)						
<7	NR		NR		4.9	
7	18	0.220	18	0.077	3.8	0.833
Histologic grade						
1–2	24		24		4.9	
3a–3b	NR	0.517	NR	0.956	4.3	0.920

OS, overall survival; CSS, cause-specific survival; PFS, progression-free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; BM, bone marrow; FLIPI, Follicular Lymphoma International Prognostic Index; LDH, lactate dehydrogenase; β2MG, β2-microglobulin; ESR, erythrocyte sedimentation rate.

the CSS of patients younger than 40 diagnosed with FL before or after 2000. Importantly, our data show that younger patients with FL had a life expectancy superior to 20 years, a useful information when counselling younger patients with FL. However, the long-term prognosis of patients diagnosed with FL before the age of 60 years remains unsatisfactory. Indeed, while the life expectancy in the EU for healthy individuals 40 years old is of 42 years (www.eurostat.com; accessed on December 2013), the projected median OS for younger patients with FL is of 24 years.

In conclusion, in parallel to the global population of patients with FL, the outcome of younger patients with this type of lymphoma has been improving over the years. However, the undeniable progress in the management of patients with FL has not resulted in a normal life expectancy for these subjects, with

Table 5. Multivariate analysis by Cox model for OS in the population of FL patients aged ≤40 years old

	HR	SE	*Z*	*P*-value	95% Confidence interval	
FLIPI	2.85	0.70	4.21	<0.0001	1.75	4.63
Era of diagnosis	0.57	0.17	−1.85	0.064	0.31	1.03

OS, overall survival; FL, follicular lymphoma; HR, hazard ratio; SE, standard error; FLIPI, Follicular Lymphoma International Prognostic Index.

Table 6. Multivariate analysis by Cox model for CSS in the population of FL patients aged ≤40 years old

	HR	SE	*Z*	*P*-value	95% Confidence interval	
FLIPI	2.65	0.69	3.77	<0.0001	1.59	4.41
Era of diagnosis	0.53	0.16	−2.04	0.042	0.29	0.97

CSS, cause-specific survival; FL, follicular lymphoma; HR, hazard ratio; SE, standard error; FLIPI, Follicular Lymphoma International Prognostic Index.

Table 7. Multivariate analysis by Cox model for PFS in the population of FL patients aged ≤40 years old

	HR	SE	*Z*	*P*-value	95% Confidence interval	
FLIPI	2.03	0.31	4.63	<0.0001	1.50	2.73
Era of diagnosis	0.69	0.12	−2.16	0.031	0.49	0.97

PFS, progression-free survival; HR, hazard ratio; SE, standard error; FLIPI, Follicular Lymphoma International Prognostic Index.

all groups of age seeing their lifespan shortened because of the disease. Also, our data indicate that prognostic factors useful in the whole population of patients with FL also apply to younger patients, and that lymphoma-specific survival is similar in young adults and in patients aged 40–60, suggesting that FL in young adults, differently from paediatric FL [21, 22], does not represent a distinct entity that needs to be treated differently. However, prospective studies are needed to delineate the clinical and biological diversity of FL across all age groups.

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disclosure

The authors have declared no conflicts of interest.

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