12. Altieri A, Gallus S, Franceschi S et al. Hormone replacement therapy and risk of lymphomas and myelomas. Eur J Cancer Prev 2004; 13: 349–351.
13. Zhang Y, Holford TR, Leaderer B et al. Prior medical conditions and medication use and risk of non-Hodgkin lymphoma in Connecticut United States women. Cancer Causes Control 2004; 15: 419–428.
14. Cerhan JR, Vachon CM, Habermann TM et al. Hormone replacement therapy and risk of non-hodgkin lymphoma and chronic lymphocytic leukemia. Cancer Epidemiol Biomarkers Prev 2002; 11: 1466–1471.
15. Nelson RA, Levine AM, Bernstein L. Reproductive factors and risk of intermediate- or high-grade B-Cell non-Hodgkin's lymphoma in women. J Clin Oncol 2001; 19: 1381–1387.
16. Schiff D, Suman VJ, Yang P et al. Risk factors for primary central nervous system lymphoma: a case-control study. Cancer 1998; 82: 975–982.
17. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res 1992; 52: 5510s–5515s.
18. Tavani A, Pregnolato A, La Vecchia C et al. A case-control study of reproductive factors and risk of lymphomas and myelomas. Leuk Res 1997; 21: 885–888.
19. Cerhan JR, Ansell SM, Fredericksen ZS et al. Genetic variation in 1253 immune and inflammation genes and risk of non-Hodgkin lymphoma. Blood 2007; 110: 4455–4463.
20. Spinelli JJ, Ng C, Weber JP et al. Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer 2007; 121: 2767–2775.
21. Talamini R, Montella M, Crovatto M et al. Non-Hodgkin's lymphoma and hepatitis C virus: a case-control study from northern and southern Italy. Int J Cancer 2004; 110: 380–385.
22. Suzuki T, Matsuo K, Ito H et al. A past history of gastric ulcers and Helicobacter pylori infection increase the risk of gastric malignant lymphoma. Carcinogenesis 2006; 27: 1391–1397.
23. Morton LM, Turner JJ, Cerhan JR et al. Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood 2007; 110: 695–708.
24. Cerhan JR, Wallace RB, Folsom AR et al. Medical history risk factors for non-Hodgkin's lymphoma in older women. J Natl Cancer Inst 1997; 89: 314–318.
25. Pfeilschifter J, Koditz R, Pfohl M et al. Changes in proinflammatory cytokine activity after menopause. Endocr Rev 2002; 23: 90–119.
26. Willett EV, Morton LM, Hartge P et al. Non-Hodgkin lymphoma and obesity: a pooled analysis from the InterLymph Consortium. Int J Cancer 2008; 122: 2062–2070.
27. Larsson SC, Wolk A. Body mass index and risk of non-Hodgkin's and Hodgkin's lymphoma: a meta-analysis of prospective studies. Eur J Cancer 2011;47: 2422–2430.
28. Banks E, Beral V, Cameron R et al. Agreement between general practice prescription data and self-reported use of hormone replacement therapy and treatment for various illnesses. J Epidemiol Biostat 2001; 6: 357–363.
29. Kropp S, Terboven T, Hedicke J et al. Good agreement between physician and self-reported hormone therapy data in a case-control study. J Clin Epidemiol 2007; 60: 1280–1287.
30. Lokkegaard EL, Johnsen SP, Heitmann BL et al. The validity of self-reported use of hormone replacement therapy among Danish nurses. Acta Obstet Gynecol Scand 2004; 83: 476–481.
31. Paganini-Hill A, Clark LJ. Comparison of patient recall of hormone therapy with physician records. Menopause 2007; 14: 230–234.
32. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. Lancet 1997; 350: 1047–1059.

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Examination of the follicular lymphoma international prognostic index (FLIPI) in the National LymphoCare study (NLCS): a prospective US patient cohort treated predominantly in community practices

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Background: Because follicular lymphoma (FL) patients have heterogeneous outcomes, the FL international prognostic index (FLIPI) was developed to risk-stratify patients and to predict survival. However, limited data exist

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regarding the role of FLIPI in the era of routine first-line rituximab (R) and R-chemotherapy regimens and in the setting of community oncology practices.

Patients and Methods: We evaluated the outcome data from the National LymphoCare Study (NLCS), a prospective, observational cohort study, which collects data on patients with FL in the United States (US) community practices.

Results: Among 1068 male and 1124 female patients with FLIPI data, most were treated in US community practices (79%); 35% were FLIPI good risk, 30% intermediate risk, and 35% poor risk. FLIPI risk groups were significant predictors of overall survival (OS) and progression-free survival (PFS) for patients who undergo watchful waiting (WW), and those who receive non-R-containing regimens, R-alone, and R-chemotherapy combinations.

Conclusions: In the setting of contemporary practice with routine R use, stratifying patients into good, intermediate, and poor FLIPI risk groups predicts distinct outcomes in terms of OS and PFS. FLIPI remains an important prognostic index in the R era and should be used in clinical practices to support discussions about prognosis.

Key words: community practice, fLIPI, follicular lymphoma, nLCS

introduction

Follicular lymphoma (FL) is the second most common form of non-Hodgkin's lymphoma (NHL); and the most prevalent indolent lymphoma in United States (US); representing 35% of adult NHL in United States and 22% worldwide [1]. Treatment outcomes have improved substantially with the introduction of rituximab (R), better sequential and combination therapies, and improved supportive measures [2, 3]. A retrospective single-institution analysis reviewing the treatment experience of patients with stage IV FL from 1972 to 2002 showed that over this time period, 5-year overall survival (OS) and failure-free survival improved from 64% to 95% and 29% to 60%, respectively [4]. However, outcomes for FL remain heterogeneous. Risk stratification of FL patients at presentation can support discussions about prognosis and theoretically could improve treatment selection by identifying patients who might require an intensified approach and those who could avoid unnecessary intervention.

Solal-Céligny et al. proposed the follicular lymphoma international prognostic index (FLIPI) as a model to predict FL survival in patients receiving chemotherapy and tested the FLIPI in FL patients diagnosed between 1985 and 1992 [5]. Using five adverse prognostic factors, age (>60 years), stage (III–IV), hemoglobin (<12 g/dl), number of nodal areas (>4), and lactate dehydrogenase (LDH) level [>upper limit of normal (ULN)], FLIPI separates patients into low/good risk (0–1 adverse factors), intermediate risk (2 factors), and high/poor risk (≥3 factors) with statistically different OS. An external validation of this model in another group of 919 patients with FL also showed significant differences in OS [5]. Although widely used in clinical trials, the role of FLIPI in routine clinical care has not been well characterized in large cohort studies with sufficient clinical and laboratory data. Therefore, we examined the FLIPI in the National LymphoCare Study (NLCS) dataset, a large national prospective observational study of newly diagnosed FL patients [6], to determine whether FLIPI maintains its prognostic significance in the modern chemoimmunotherapy era especially, in the setting of US-based clinical practices.

patients and methods

The NLCS is a prospective, observational study of patients with FL in the US sponsored by Genentech, Inc. (South San Francisco, CA) and Biogen Idec (Cambridge, MA). The NLCS has an advisory board composed of academic investigators and a patient advocate, some of whom co-authored this manuscript (TPM, JWF, ADZ, BKL, JRC, HD, and CRF). The advisory board participated in all phases of the study, including initial protocol design, prospective determination of data to be collected, and consideration of participating sites. The advisory board meets quarterly, has full access to data listings, and collaborated with the investigator (AKN) and the sponsor regarding interpretation and publication of the data. The design, analysis, and data interpretation of this study adhered to scientific standards and guidelines for comparative effectiveness analysis that build upon initiatives to improve the quality and transparency of clinical science [7, 8]. This article was written *de novo* by the investigator and the members of the advisory board following approval of a protocol with pre-specified end-points, hypotheses, and plans for analysis.

A total of 2742 patients were recruited from academic and community oncology practices between March 2004 and March 2007 at 265 sites in the US. 2192 assessable patients with non-missing FLIPI scores were included in the analysis. Fifteen patients were ineligible, primarily due to missing date of diagnosis. Final selection of academic and community sites and the data collection occurred as previously described, was determined by study sponsors based on the responses to a survey assessing capability to participate in an observational study of FL. Questions included number of newly diagnosed FL patients seen annually, logistics and support for clinical research, and previous experience with sponsored clinical research [6]. All patients signed a written informed consent before participation, and the protocol was approved by a designated institutional review board at each institution. At enrollment, all patients were within 6 months from their initial FL diagnosis and had no prior history of lymphoma. Per protocol, to minimize potential patient selection bias, investigators at participating sites were encouraged to invite all eligible patients to participate in the study consecutively. The eligibility criteria included age ≥18 years and did not exclude patients based on the performance status (PS) or comorbidities. There was no central pathology review; the local pathology report defined FL diagnosis after investigator education on World Health Organization classification system definitions of FL [9]. Grade and evidence for concurrent second lymphoma were evaluated when available.

Patients were evaluated and treated according to each physician's standard practice, without study-specific treatments, visits, or evaluations required either at baseline or during the course of the study. Collected

information included demographics, clinical data (including PS, stage, and number of nodal and extra-nodal sites), routine laboratory studies including LDH, serial management strategies, response to treatment, and outcomes including relapse and death. From the inception of the NLCS study, the treating physicians were requested to obtain LDH at diagnosis with the primary objective of calculating FLIPI. Follow-up data regarding treatment and outcomes (including response, progression, and survival) were actively solicited from providers and collected quarterly. Enrolled patients are to be observed for up to 10 years from enrollment or until death, withdrawal of consent, or loss to follow-up. Enrollment sites were categorized as academic or community practices based on self-report.

FLIPI score and risk groups

For each patient, a FLIPI score was assigned according to the algorithm defined by Solal-Céligny et al. as the sum of each of the five risk factors at diagnosis. The risk groups were classified for 191 patients with some missing FLIPI components where missing data did not impact the risk categorization to a FLIPI group (e.g. a patient with 1 missing FLIPI component and 0 risk factors for the four non-missing FLIPI components would be classified as low/good risk).

outcomes

overall survival

OS was calculated as the number of days from the date of diagnosis up to and including the date of death from any cause. For patients who were not confirmed dead at the time of analysis, OS was censored at the date that the patient was last known to be alive. For patients who discontinued from the study, OS was censored at the date of discontinuation. For patients who had not discontinued enrollment, OS was censored at the last study assessment recorded in the database or last contact.

progression-free survival

PFS was calculated as the number of days from the date of diagnosis up to and including the date of the first event, which was either disease progression as assessed by the treating physician or death from any cause. The receipt of new antilymphoma treatment was not considered an event since treatment in community practice did not require progression. PFS for patients who had not yet experienced an event at the time of analysis was censored at the date of the last recorded response assessment.

time to next treatment

Time to next (subsequent) treatment (TTNT) was defined as the number of days from the date of treatment initiation [for patients receiving

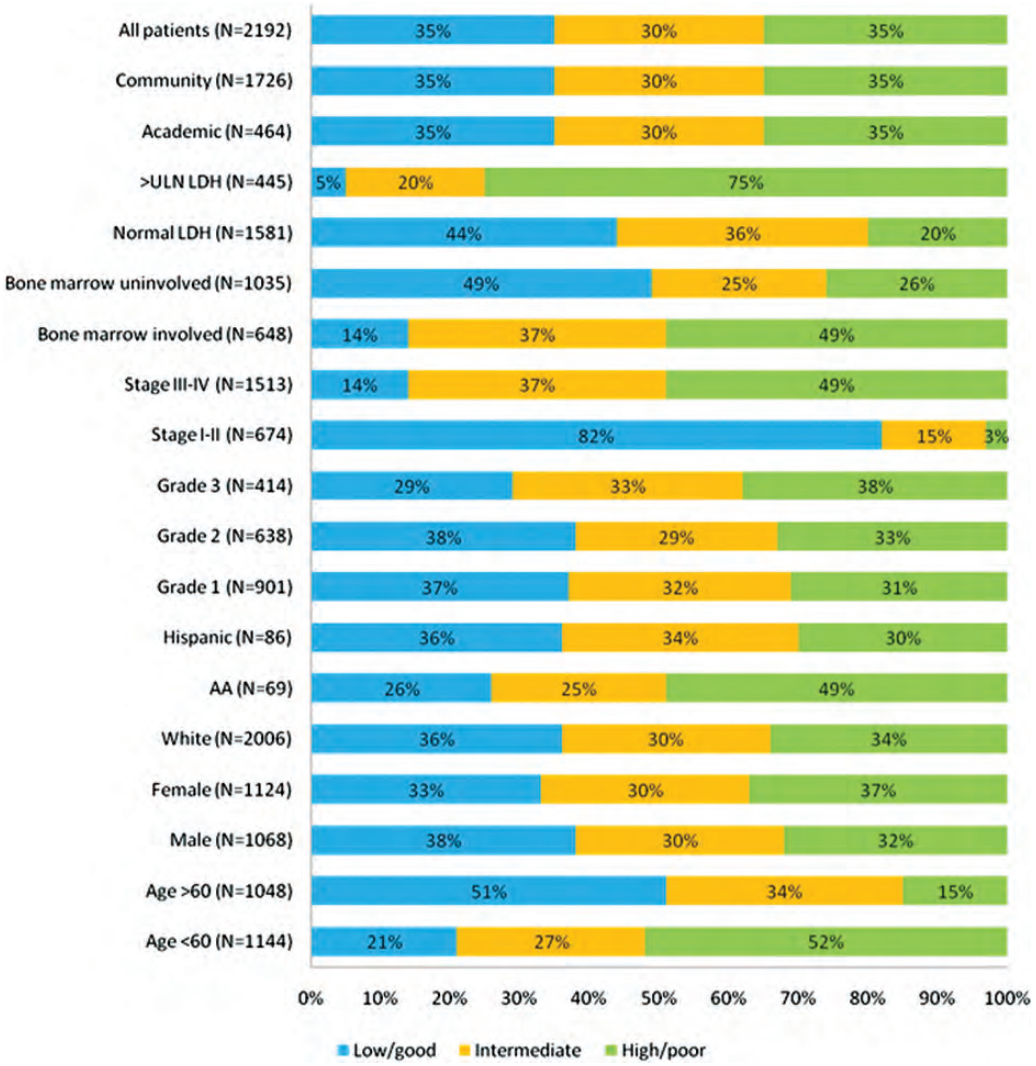

Figure 1. Distribution of FLIPI risk groups in the overall sample and in specific demographic and clinical subgroups.

watchful waiting (WW), this is the date the physician recorded as selecting a WW management strategy] up to and including the date of initiation of the next treatment for any reason. For patients who had no record to indicate the initiation of a subsequent treatment, the censor of next treatment was assigned. The date of censoring was defined as the last study assessment or last contact recorded in the database, or the date of discontinuation for patients who had discontinued from the study.

statistical analysis

Patient characteristics at diagnosis were summarized using descriptive statistics by FLIPI risk groups and for all patients combined, and Pearson's chi-square test was carried out to examine the difference in the baseline characteristics between FLIPI risk groups. For the outcomes of OS, PFS, and TTNT, the prognostic value of the FLIPI risk groups was validated by estimating survival function using the Kaplan–Meier method and calculating the hazard ratios (HR) from the Cox proportional hazards model with the FLIPI risk group as the single-independent variable. Additional Cox proportional hazards analysis was examined for each outcome to evaluate the predictive function of FLIPI adjusting for the effects of treatment setting (academic versus community), gender, and race. The FLIPI was examined for all treatments combined and specific treatment regimens.

results

A total of 2192 assessable patients with identified FLIPI status were included in the analyses. Among the 1068 male and 1124 female patients, 52% were >60 years, 69% were stage III–IV, 22% had Hb < 12 g/dl, 37% had >4 nodal areas involved, and 22% had elevated LDH levels. Most patients were white (92%), treated in US community practices (79%), and had Eastern Cooperative Oncology Group (ECOG) PS of 0/1 (67%/28%). Approximately one-third of the patients were in each FLIPI risk group (Figure 1). One-third of the patients in the low/good FLIPI group had none of the five risk factors. In the high-/poor-risk FLIPI group, 4.8% patients had five risk factors, 25.8% had four risk factors, and 69.4% had three risk factors. A higher percentage in the poor-risk FLIPI group had follicular grade 3, B symptoms, ECOG score of 1 or more, extra-nodal sites, and bone marrow involvement ($P < 0.05$). The distribution of FLIPI risk groups in the overall sample and in specific demographic and clinical subgroups is summarized in Figure 1. The distribution of patients in the FLIPI risk groups was similar between academic and community practices.

As shown in Table 1, approximately two-thirds of the patients were initially treated with R either as a monotherapy (13.5%) or R in combination with chemotherapy (51.6%); while 17.0% underwent a WW strategy; and 15.3% received non-R containing therapies. Compared with patients in good or intermediate FLIPI risk groups, a higher percentage of patients in the poor-risk FLIPI group were treated with immunochemotherapy, and fewer underwent WW strategy.

Kaplan–Meier survival curves are presented in Figure 2 for the three outcomes (i.e. OS, PFS, and TTNT) for the overall patient population and for patients who received R-containing regimens. With a median follow-up of 57.9 months, OS was significantly different between FLIPI groups. Furthermore, PFS and TTNT were best in good-risk FLIPI patients compared with those in the intermediate- and poor-risk categories.

Table 1. Initial treatment by the FL international prognostic index (FLIPI) risk group

Treatment modality	FLIPI risk group			Total *N* (%)
	Good *N* (%)	Intermediate *N* (%)	Poor *N* (%)	
	770 (100)	666 (100)	756 (100)	2192 (100)
Watch and wait	170 (22.1)	129 (19.4)	74 (9.8)	373 (17.0)
R/R-containing regimen				
R-Mono	95 (12.3)	88 (13.2)	113 (14.9)	296 (13.5)
R-Chemo	304 (39.5)	348 (52.3)	480 (63.5)	1132 (51.6)
Combined modality–XRT	42 (5.5)	7 (1.1)	4 (0.5)	53 (2.4)
Combined modality–BMT	1 (0.1)		1 (0.1)	2 (0.1)
Any of the above	442 (57.4)	443 (66.5)	598 (79.1)	1483 (67.7)
Non-R-containing regimens				
Chemo	18 (2.3)	21 (3.2)	23 (3.0)	62 (2.8)
XRT	99 (12.9)	9 (1.4)	6 (0.8)	114 (5.2)
Combined modality–XRT	2 (0.3)			2 (0.1)
Investigational	31 (4.0)	61 (9.2)	52 (6.9)	144 (6.6)
Other	8 (1.0)	3 (0.5)	3 (0.4)	14 (0.6)
Any of the above	158 (20.5)	94 (14.1)	84 (11.1)	336 (15.3)

The unadjusted and adjusted HR with 95% confidence intervals (CI) by the FLIPI group for OS, PFS, and TTNT are shown in Table 2. Compared with the good-risk group, the unadjusted HR for OS was 2.37 for the intermediate-risk group and 6.17 for the poor-risk group. In this cohort, there were significant differences in OS (but not PFS or TTNT) by treatment setting [HR community versus academic (95% CI) = 1.65(1.23, 2.21)] for OS, 1.01 (0.86, 1.19) for PFS, and 1.05 [0.89, 1.25] for TTNT). There were no differences in any outcome across gender categories. As seen previously by Nabhan et al. [10], PFS was not significantly different between African American and White but was improved in Hispanic patients (HR = 0.53 [0.33, 0.83] vs White). The Cox proportional hazards models adjusted for treatment setting, gender, and race/ethnicity produced similar results to unadjusted models (Table 2).

The prognostic value of FLIPI was further assessed with patients in six treatment subgroups: (R-containing treatment; non-R-containing treatment; single-agent R (R-mono); R, cyclophosphamide (Baxter Healthcare Corporation, IL, USA), doxorubicin (Pfizer Inc, NY, USA) (Adriamycin), vincristine (Hospira Inc, IL, USA) and prednisone (R-CHOP); R, cyclophosphamide, vincristine and prednisone (R-CVP); and WW using a Cox proportional hazards model with adjustment for treatment setting (Table 3). In patients provided with R-containing treatment, there was an incremental increase in the usage of therapy from FL grade 1 to grade 2 to grade 3 (R-CVP–8.7%, 9.7%, and 17.4%, and R-CHOP–21.4%, 27.1%, and 31.4%, respectively). FLIPI appears to be a useful predictor across treatment strategies for events of interest OS, PFS, and TTNT (supplementary Tables S1 and S2 available at *Annals of Oncology* online, Figure 3 and supplementary Figure S1, available at *Annals of Oncology* online).

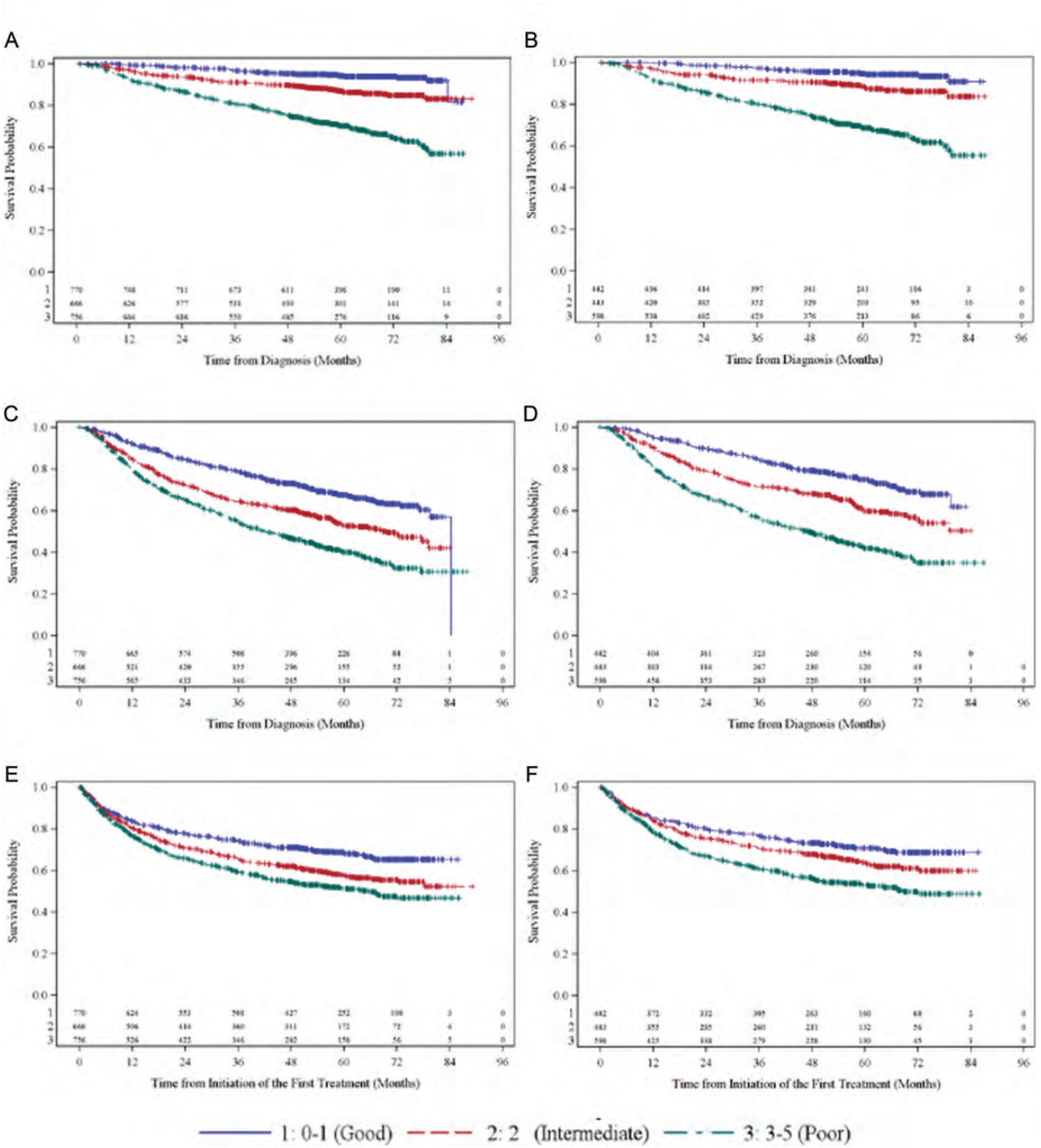

Figure 2. Kaplan–Meier (K–M) survival functions for OS, PFS, and time to next treatment (TTNT) by the FLIPI risk group. (A) Overall survival (OS) by the FL international prognostic index (FLIPI) risk groups for all treatments. (B) OS by FLIPI risk groups for R-containing regimens. (C) Progression-free survival by FLIPI risk groups for all treatments. (D) Progression-free survival by FLIPI risk groups for R-containing regimens. (E) Time to next treatment by FLIPI risk groups for all treatments. (F) Time to next treatment by FLIPI risk groups for R-containing regimens.

discussion

FLIPI is a reproducible prognostic index based on routinely available clinical data. This index allows for risk stratification, predicting OS outcomes for patients treated with chemotherapy. One potential shortcoming of FLIPI is that the scoring system was developed in the pre-R-era questioning its significance in modern era. Prognostic models for FL: the ILI [11], IPI [12], and FLIPI [5] were compared by Perea et al. [13], demonstrating an overall concordance between the three classification systems of 54% for good-risk groups, 10% for intermediate-risk groups, and 36% for poor-risk groups. FLIPI

Table 2. Hazards ratios (HR) for progression-free survival (PFS), time to next treatment (TTNT) and overall survival (OS), by FLIPI risk groups ($n = 2192$)

Outcome/FLIPI risk group	Unadjusted hazard ratio (HR, 95% CI)	*P*	Adjusted[a] HR (95% CI)	*P*	Adjusted[b] HR (95% CI)	*P*
OS						
Intermediate ($N = 666$)	2.37 (1.64, 3.41)	<0.0001	2.38 (1.65, 3.43)	<0.0001	2.41 (1.67, 3.47)	<0.0001
Poor ($N = 756$)	6.17 (4.47, 8.53)	<0.0001	6.24 (4.51, 8.62)	<0.0001	6.33 (4.58, 8.76)	<0.0001
PFS						
Intermediate ($N = 666$)	1.63 (1.36, 1.94)	<0.0001	1.63 (1.37, 1.94)	<0.0001	1.63 (1.37, 1.95)	<0.0001
Poor ($N = 756$)	2.36 (2.01, 2.78)	<0.0001	2.37 (2.01, 2.79)	<0.0001	2.35 (2.00, 2.77)	<0.0001
TTNT						
Intermediate ($N = 666$)	1.39 (1.17, 1.66)	0.0002	1.39 (1.17, 1.66)	0.0003	1.40 (1.17, 1.67)	0.0002
Poor ($N = 756$)	1.71 (1.45, 2.02)	<0.0001	1.72 (1.45, 2.03)	<0.0001	1.71 (1.45, 2.03)	<0.0001

[a]Adjusted for treatment setting (academic or community).
[b]Adjusted for treatment setting, sex, and race.

Table 3. Hazards ratios (HR)[a] for OS, PFS, and TTNT, by treatment strategy

Treatment/ risk group	Overall survival (OS) HR (95% CI)	Progression-free survival (PFS) HR (95% CI)	Time to next treatment (TTNT) HR (95% CI)
All patients ($N = 2190$)			
Intermediate	2.38 (1.65, 3.43)	1.63 (1.37–1.94)	1.39 (1.17–1.66)
Poor	6.24 (4.51, 8.62)	2.37 (2.01–2.79)	1.72 (1.45–2.03)
Watchful waiting (W&W) ($N = 372$)			
Intermediate	2.73 (1.32–5.67)	1.82 (1.33–2.49)	1.54 (1.11–2.14)
Poor	4.46 (2.15–9.26)	1.96 (1.38–2.77)	1.47 (1.00–2.16)
R-Mono ($N = 296$)			
Intermediate	6.38 (1.84–22.03)	1.61 (1.02–2.55)	0.84 (0.51–1.37)
Poor	14.55 (4.50–47.03)	2.63 (1.74–3.99)	1.87 (1.25–2.80)
R-CVP ($N = 264$)			
Intermediate	1.35 (0.41–4.44)	1.28 (0.64–2.57)	1.37 (0.69–2.70)
Poor	5.94 (2.36–14.99)	3.69 (2.11–6.45)	2.34 (1.32–4.15)
R-CHOP ($N = 583$)			
Intermediate	1.75 (0.77–3.96)	1.65 (1.09–2.50)	1.22 (0.83–1.80)
Poor	4.81 (2.37–9.75)	2.48 (1.70–3.63)	1.49 (1.04–2.13)
R/R-containing regimen ($N = 1482$)			
Intermediate	2.31 (1.42–3.76)	1.67 (1.31–2.14)	1.29 (1.01–1.63)
Poor	7.09 (4.63–10.86)	3.01 (2.41–3.76)	1.82 (1.47–2.26)
Non-R-containing regimen ($N = 336$)			
Intermediate	2.47 (1.04–5.90)	2.05 (1.32–3.17)	2.21 (1.40–3.47)
Poor	4.83 (2.21–10.56)	2.72 (1.78–4.15)	2.71 (1.73–4.24)

Reference group––good risk patients (HR 1.00).
[a]Adjusted for treatment setting (academic or community).

better defined the poor-risk group than IPI and ILI, and was thus considered to be the more useful prognostic tool for patients with FL. Our data indicate that a FLIPI score ≥3 defines a population of patients who have worse survival across all common management strategies in the US even in the era of R use.

More recently, FL predictive models for risk stratification have been validated in both the population-based settings [14] and the R era [15]. A new prognostic model, FLIPI2 [16], was also developed in a prospective study using PFS as a surrogate for OS. In the FLIPI2, β-2M > ULN, a lymph node measuring >6 cm, bone marrow involvement, Hb < 12 g/dl, and age >60 years were the five characteristics that were predictive of increased risk of death. While the FLIPI2 provides a useful prognostic model for FL, the study involved 1093 FL cases registered between 2003 and 2005 from Europe and the United States, utilized a short-term surrogate outcome (PFS), and involved covariates that may not be routinely collected in clinical practices such as β-2M. Because serum β-2M value at baseline was not available in the NLCS dataset, we were unable to compare FLIPI with FLIPI2. While inclusion of serum β-2M may provide more meaningful indicator disease biology, it can be confounded by renal insufficiency and may not be readily available or collected in community-based practices. Another limitation is the absence of central pathology review. A potential consequence of such limitation is the inclusion of grade 3A & 3B FL as one category.

There are a few unique salient features specific for the NLCS data. It included patients in a community setting and included different practices of WW, R-therapy, R-chemo regimens used in clinical practices. Our findings validate the findings of the use of FLIPI in R-chemotherapy clinical trials [15, 17]. However, it is well known that the patient selection in clinical trials can influence treatment outcome that may not be applicable to patients in clinical practices. The NLCS included patients in a community setting with varying use of WW, R-monotherapy, and R-chemotherapy regimens as administered in clinical practices and thus demonstrates the value of the FLIPI in general clinical practice. This study reflects a 'real world' snapshot of common practice patterns.

A potential limitation of the NLCS is the introduction of unintentional bias resulting from site and subject selection that makes this cohort differ from the general population of FL patients. We have previously shown that the FL patients in the NLCS are quite similar to FL patients in the 2004–2007 US Surveillance, Epidemiology and End Results (SEER) registry [6]. Moreover, FLIPI stratifies the NLCS patients into three groups, each comprising ~1/3 population, similar to its performance in the original study that defined the FLIPI, and these findings from the NLCS dataset produced HR for OS in concordance with the original FLIPI study [5]. Given the similar demographics to the SEER registry and the survival outcomes were in concordance with the

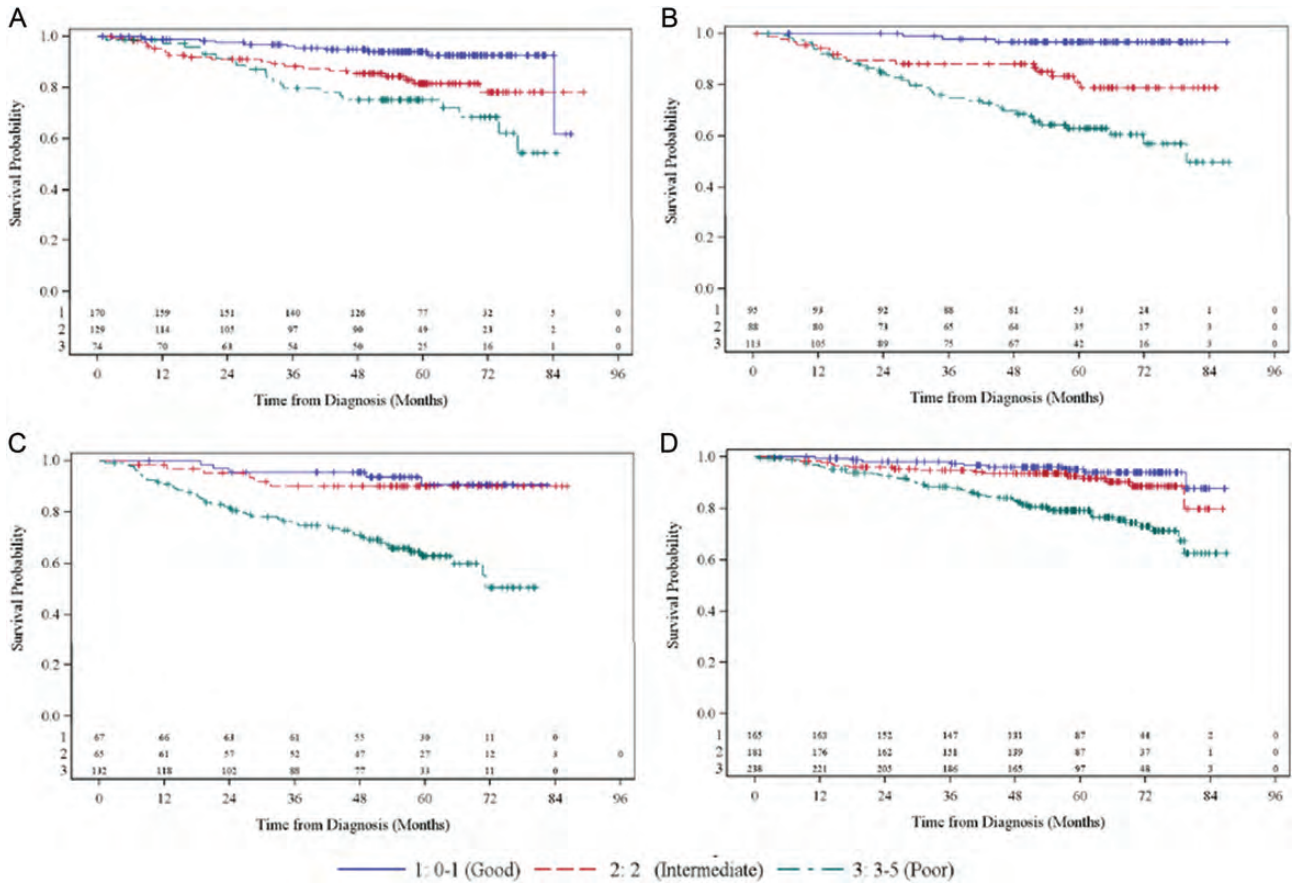

Figure 3. K–M survival functions for OS by the FL international prognostic index (FLIPI) risk group and treatment. (A) OS by FLIPI risk groups for watch and wait patients. (B) OS by FLIPI risk groups for patients treated with R-monotherapy. (C) OS by FLIPI risk groups for patients treated with R-CVP. (D) OS by FLIPI risk groups for patients treated with R-CHOP.

original FLIPI study, the observations made from this registry may be generalized and reflect the 'real world' FL patients in the US. However, this observational study is limited by variations in practice patterns for patients treated in the United States, variations in patient follow-up due to the lack of protocol pre-specified treatment strategies. While data generated from randomized, controlled trials is the most desirable to formulate clinical decisions, completing such trials may not always be possible due to cost considerations and the length of time involved. Data from prospective observational studies and well-defined end-points, such as the NLCS, can help to corroborate the results of data from trials in which observational studies yield similar findings. FLIPI remains a simple, validated index demonstrating discriminatory power to aid in defining poor-risk patients across treatment strategies and provide estimates of prognosis for patients treated in community practices.

Our prospectively collected data show that FLIPI is a valid and important prognostic tool for patients receiving contemporary immunochemotherapy regimens. It is encouraging to acknowledge that US cooperative groups are using FLIPI to stratify patients and design risk-specific studies in FL. The results from this NLCS study indicate that this approach is reasonable and needed in the current immunochemotherapy era. We propose that FLIPI should be used in community practices to provide prognostic information for patients with FL receiving commonly administered modern therapies and to support discussions regarding expected treatment outcomes. Future studies are needed to determine whether patients in different FLIPI risk categories should be treated differently.

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disclosures

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references

1. Ganti A, Bociek R, Bierman P et al. Follicular lymphoma: expanding therapeutic options. Oncology (Huntingt) 2005; 19: 213–228.
2. Fisher RI, Kaminski MS, Wahl RL et al. Tositumomab and Iodine-131 Tositumomab produces durable complete remissions in a subset of heavily pretreated patients with low-grade and transformed non-Hodgkin's lymphomas. J Clin Oncol 2005; 23: 7565–7573.
3. Swenson WT, Wooldridge JE, Lynch CF et al. Improved Survival of Follicular Lymphoma Patients in the United States. J Clin Oncol 2005; 23: 5019–5026.
4. Liu Q, Fayad L, Cabanillas F et al. Improvement of Overall and Failure-Free Survival in Stage IV Follicular Lymphoma: 25 Years of Treatment Experience at the University of Texas M.D. Anderson Cancer Center. J Clin Oncol 2006; 24: 1582–1589.
5. Solal-Celigny P, Roy P, Colombat P et al. Follicular lymphoma international prognostic index. Blood 2004; 104: 1258–1265.
6. Friedberg JW, Taylor MD, Cerhan JR et al. Follicular lymphoma in the United States: first report of the national LymphoCare study. J Clin Oncol 2009; 27: 1202–1208.
7. Eden J, Institute of Medicine (US). Committee on reviewing evidence to identify highly effective clinical services. Knowing what works in health care: a roadmap for the nation. Washington, DC: National Academies Press 2008.
8. Simera I, Altman DG, Moher D et al. Guidelines for reporting health research: the EQUATOR network's survey of guideline authors. PLoS Med 2008; 5: e139.
9. Matasar MJ, Zelenetz AD. Overview of lymphoma diagnosis and management. Radiol Clin North Am 2008; 46: 175–198.
10. Nabhan C, Taylor M, Hirata J et al. Racial disparities in disease presentation, treatment, and response rates of follicular lymphoma (FL) in the United States (US): report from the National LymphoCare study (NLCS). ASH Annu Meeting Abstr 2009; 114: 1381.
11. Federico M, Vitolo U, Zinzani PL et al. Prognosis of follicular lymphoma: a predictive model based on a retrospective analysis of 987 cases. Intergruppo Italiano Linfomi. Blood 2000; 95: 783–789.
12. A predictive model for aggressive non-Hodgkin's lymphoma. The international non-Hodgkin's lymphoma prognostic factors project. N Engl J Med 1993; 329: 987–994.
13. Perea G, Altes A, Montoto S et al. Prognostic indexes in follicular lymphoma: a comparison of different prognostic systems. Ann Oncol 2005; 16: 1508–1513.
14. van de Schans SAM, Steyerberg EW, Nijziel MR et al. Validation, revision and extension of the Follicular Lymphoma International Prognostic Index (FLIPI) in a population-based setting. Ann Oncol 2009; 20: 1697–1702.
15. Buske C, Hoster E, Dreyling M et al. The follicular lymphoma international prognostic index (FLIPI) separates high-risk from intermediate- or low-risk patients with advanced-stage follicular lymphoma treated front-line with rituximab and the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) with respect to treatment outcome. Blood 2006; 108: 1504–1508.
16. Federico M, Bellei M, Marcheselli L et al. Follicular lymphoma international prognostic index 2: a new prognostic index for follicular lymphoma developed by the international follicular lymphoma prognostic factor project. J Clin Oncol 2009; 27: 4555–4562.
17. Overman MJ, Feng L, Pro B et al. The addition of rituximab to CHOP chemotherapy improves overall and failure-free survival for follicular grade 3 lymphoma. Ann Oncol 2008; 19: 553–559.

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Adjuvant therapy with cetuximab for locally advanced squamous cell carcinoma of the oropharynx: results from a randomized, phase II prospective trial

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Background: Cetuximab combined with radiotherapy (RT) is a treatment option for head and neck cancer. The objectives of this randomized, phase II trial were to evaluate the efficacy and safety of cetuximab maintenance therapy following definitive RT with concomitant cetuximab in patients with oropharyngeal cancer.
Patients and methods: Ninety-one patients with stage III–IV M0 oropharyngeal tumors were randomly assigned to the treatment with accelerated concomitant boost RT (69.9 Gy) + cetuximab or the same treatment with the addition of 12 consecutive weeks of cetuximab maintenance therapy. The primary end point was locoregional control (LRC) at 1 year.

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