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## Quality of life appears similar between survivors of indolent and aggressive non-Hodgkin lymphoma

Anne H. Blaes<sup>1</sup>, Linan Ma<sup>2</sup>, Yan Zhang<sup>2</sup>, and Bruce A. Peterson<sup>1</sup>

<sup>1</sup> Division of Hematology/Oncology/Transplantation, Department of Medicine, University of Minnesota, Minneapolis, MN, USA

<sup>2</sup> Biostatistics and Informatics Core, Masonic Cancer Center, University of Minnesota, Minneapolis, MN, USA

### Abstract

Few studies have examined the quality of life (QOL) in survivors of non-Hodgkin lymphoma (NHL). A total of 109 patients with NHL (58 aggressive [AGG], 51 indolent [IND]) completed two health-related QOL assessments using the Medical Outcomes Study 36-Item Short-Form Healthy Survey (MOS SF-36) and the Functional Assessment in Cancer Therapy – Fatigue (FACT-F). Scores between IND and AGG were compared using a two-sample *t*-test. Multiple linear regression was performed to account for any potentially explanatory variables. Overall, 70.6% had received chemotherapy and 55% had received immunotherapy. Some 17.6% of the IND group had received no therapy. The overall physical and mental component QOL scores of the SF-36 did not differ between survivors. Physical function in survivors of IND was significantly better when compared with that of AGG NHL. Our study reports a similar overall QOL between survivors of IND and AGG NHL. Physical function, however, may be more impaired in survivors of AGG NHL.

### Keywords

Quality of life; non-Hodgkin lymphoma; lymphoma; cancer survivorship

### Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common cancer in the United States [1 – 3]. It encompasses a heterogeneous group of diseases with an overall 5-year survival of 50–60%. Disease aggressiveness in non-Hodgkin lymphoma ranges from indolent B-cell lymphomas to more aggressive lymphomas such as diffuse large B-cell lymphoma [4,5]. Patients with indolent lymphoma are typically considered incurable with standard therapeutic approaches. Their disease is typified by a chronic course with repeated relapses,

Correspondence: Anne H. Blaes, MD, University of Minnesota, 420 Delaware Street, S.E., MMC 480, Minneapolis, MN 55455, USA. Fax: 612-626-1441. blaes004@umn.edu.

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treatment, and progression, despite therapy. Patients often experience unpredictable periods in which they wait anxiously for the expected, yet unpredictable, return of their disease. Median survival is usually 5–10 years, although some patients can live past 20 years. In contrast, patients with aggressive lymphomas tend to have acute presentations with more rapid progression than the indolent entities. Nevertheless, they are often cured of their disease with combination chemotherapy; in the event of treatment failure, however, survival is usually measured in months rather than years [6].

Few studies have examined the functional limitations, physical health, mental health, and general quality of life in cancer survivors of various types of non-Hodgkin lymphoma. Despite more than 65 000 cases of non-Hodgkin lymphoma annually [1,7–9], few data exist on the quality of life specifically in these patients. While some data suggest that quality of life in adult survivors of NHL is similar to that of the general population, other studies disagree with this assessment, identifying specific areas for concern, including fatigue, sexual dysfunction, and overall depression and post-traumatic stress [6,10–12].

With the rising number of cancer survivors of both indolent and aggressive diseases and the expected increase in NHL incidence rates given the rapidly aging population [13], there is a need to evaluate and better understand the health-related quality of life in these patients. We performed a cross-sectional study to evaluate the quality of life in cancer survivors with indolent B-cell lymphomas and more aggressive forms of NHL such as diffuse large B-cell lymphoma. Given the repetition of increased numbers of treatment, the emotional burden of NHL, and potential physical impact of having NHL, we hypothesized that patients with indolent NHL > 1 year from diagnosis and not on active therapy would be more likely to suffer from fatigue and psychological impairment.

## Methods

All patients who were diagnosed and treated for NHL at the University of Minnesota, Masonic Cancer Center between 1995 and 2006 were eligible for participation in this study. The study was limited to individuals who were at least 1 year from initial diagnosis of NHL, were at least 3 months from any active chemotherapy, had a willingness to participate in the surveys, and were at least 18 years of age. Survivors of NHL who were less than 1 year from initial diagnosis, were treated with allogeneic stem cell transplant, or had developed a new primary malignancy since NHL diagnosis were excluded. In total, 143 patients were deemed eligible for participation in this study.

Patients were contacted in two ways notifying them they were eligible for participation in this study and providing opportunities to participate. First, the responsible treating physician sent their patients letters informing them about the study. If they were interested in participating, patients could mail back an addressed postcard indicating that they would like to participate in the study through the mail. It was explained that, by returning a completed questionnaire and signing a consent form, the patient agreed to participate and consented to linkage of the questionnaire data with information about their disease and treatment history in their medical record. Patients were assured that non-participation would not have any consequence for their follow-up care or treatment. If the questionnaire was not returned

within 2 months, then a reminder letter was sent together with an additional copy of the questionnaire. Returned questionnaires did not contain any explicit identifiers (i.e. names) but, rather, were coded by number for purposes of data collection tracking and linkage with the medical record. Second, if patients were still being seen and followed in the Masonic Cancer Center by their treating physician, they were notified at routine follow-up visits that they were eligible to participate in the study. After obtaining signed consent, the patients were given two questionnaires to complete, and return via the mail.

### Study measures

All consenting and eligible patients were asked to complete two health-related quality of life questionnaires, the Functional Assessment in Cancer Therapy – Fatigue (FACT-F) and Medical Outcomes Study 36-Item Short-Form Healthy Survey (MOS SF-36), on one occasion. The FACT-F is a well-established, short one-page multi-item scale question that specifically focuses on fatigue in cancer patients [14]. The SF-36 is another survey that assesses eight subsets and two summary scores related to quality of life [15–17]. The eight subsets include social functioning, physical function, mental health, role physical, general health, bodily pain, vitality, and emotional scores. The General Health (GH) scale provides a self-assessment of overall health. The Physical Functioning (PF) scale assesses physical limitations such as walking distances and climbing stairs, while the Role Physical (RP) focuses more specifically on physical limitations on physical activities. Bodily Pain measures pain as well as its impact on daily activities. The Mental Health score evaluates anxiety and psychological well-being, while the Role Emotional scale measures the impact of mental health on daily activities. The Social Functioning scale measures one's ability to engage in social activities. Two higher order component or summary scores for physical and mental health also were calculated using these numbers. By following established algorithms, the scores were standardized to age-specific 1998 population norms by using  $z$  score standardization and norm-based transformation of each scale's  $z$  score [18]. As a result, a mean of 50 represents the population average for a given scale, with each point below or above the mean indicating one-tenth of a standard deviation. For all scales, a higher value indicates a higher quality of life.

Patient and tumor characteristics were collected through medical record abstraction. These characteristics included age, sex, performance status at the time of diagnosis, performance status at the time of survey, stage at diagnosis, presence of B symptoms at diagnosis, remission status at the time of survey, use of chemotherapy (yes/no [Y/N]), radiation (Y/N), surgery (Y/N), or immunotherapy (Y/N), use of an autologous stem cell transplant (Y/N), comorbidities as defined by the Charlson comorbidity index [19], time from diagnosis to first treatment, and time from last treatment to completion of the survey.

Survivors with small lymphocytic lymphoma or B-cell chronic lymphocytic leukemia (CLL/SLL), lymphoplasmacytic lymphoma, follicular lymphoma, and marginal zone B-cell lymphoma were identified as individuals with indolent NHL. Survivors with diffuse large B-cell, anaplastic large cell, mantle cell, and Burkitt lymphoma were identified as individuals with aggressive lymphoma.

## Statistics

Patient characteristics including demographics and disease status between indolent and aggressive NHL groups were compared using a two-sample *t*-test or Wilcoxon rank-sum test for continuous variables and  $\chi^2$  test or Fisher's exact test for categorical variables. The differences in composite Physical and Mental SF-36 scores and FACT-F scores between the two groups were evaluated using a two-sample *t*-test or Wilcoxon rank-sum test. The association between types of NHL and quality of life scores from SF-36 and FACT-F questionnaires was further evaluated by multiple linear regression analysis, adjusting for demographic (age) and clinical variables (time since diagnosis, use of chemotherapy, and time from last treatment to survey). A second analysis was performed excluding the patients who had not received any therapy (data not shown). A *p*-value of less than 0.05 was considered statistically significant.

The protocol and analysis were approved by the University of Minnesota Institutional Review Board. All patients provided written informed consent according to the Declaration of Helsinki.

## Results

Using the eligibility criteria, 143 patients were deemed eligible for the study. Of these 143 patients, 109 (75%) agreed to participate and complete the questionnaires. Fifty-one of 109 (47%) had a diagnosis of indolent NHL (IND) while 58 of 109 (53%) had a diagnosis of aggressive NHL (AGG). Patient demographics and characteristics are presented in Table I.

The mean (SD) age of study participants was 58.9 (14.1) years [61.1 (12.2) years IND and 56.9 (15.4) years AGG, *p* = 0.1190]; 48.6% were female (52.9% IND, 44.8% AGG, *p* = 0.3977); 74.3% were in complete remission at the time of the survey (52.9% IND, 93.1% AGG, *p* < 0.0001); 50.5% had no comorbidities at the time of the survey (45.1% IND, 55.2% AGG, *p* = 0.0010); 33.9% had two or more comorbidities at the time of the survey (49.0% IND, 20.6% AGG); 70.6% had received chemotherapy (43.1% IND, 94.8% AGG, *p* < 0.0001) and 55.0% had received immunotherapy (31.4% IND, 75.9% AGG, *p* < 0.0001). About half of the patients in both groups were treated with radiation, and almost no patients had been treated surgically; 17.6% of IND had received no therapy; 3.4% of patients with AGG NHL had been treated with an autologous stem cell transplant, compared to 0% in the IND NHL group (*p* = 0.4967).

All of the patients completed both the SF-36 and the FACT-F quality of life assessments. The results of these surveys are summarized in Table II. The median score on the FACT-F was 45.0 out of a possible total score of 52.0 (8.0–52.0). The results were slightly higher, indicating better quality of life, for those with indolent NHL (median 47.0) as compared with aggressive NHL (median 43.0); however, these results were not significant (*p* = 0.118).

On the SF-36 assessment, the norm-based Physical Composite Score and Mental Composite Score were similar between those with aggressive and indolent NHL. The median Mental Composite Score for all NHL survivors was 54.2 (10.8–65.8) with a score of 54.6 for those

with IND NHL and 53.3 for those with AGG NHL ( $p = 0.2425$ ). The median Physical Composite Score for all NHL survivors was 51.8 (11.2–66.5) with a score of 52.7 and 50.6 for those with IND and AGG NHL, respectively ( $p = 0.1955$ ). Of the eight subscales evaluated, only Emotional Role and Role Physical differed between those with IND and AGG NHL. The overall median score for Emotional Role, which assesses the impact of mental health on daily activities, was 55.9 (17.0–55.9) with a median score of 55.9 for those with IND NHL and 48.1 for those with AGG NHL ( $p = 0.0246$ ). The overall median score for Role Physical was 52.0 (17.7–56.9) with a median score of 56.9 and 49.5 for those with IND and AGG NHL ( $p = 0.0158$ ), respectively. In both of these cases, those with AGG NHL had poorer scores, indicating that their mental health may impact daily activities and that they may have physical limitations on physical activity. When adjusting for age, time from last treatment to the survey, use of chemotherapy, and number of comorbidities, Physical Function (specifically addressing physical limitations) was significantly more impaired in those with aggressive NHL, as compared to those with indolent NHL ( $p = 0.0479$ ). When the analysis was performed again after excluding the patients who had not received any treatment (all of whom had IND NHL), Physical Function continued to be more impaired in those with AGG NHL. No other assessments were significantly different between the two NHL groups after controlling for those factors in multiple linear regression. With a normative population mean quality of life score of 50 (standard deviation of 10), the patients in our study had quality of life scores comparable to the general population.

## Discussion

In NHL, three studies have been published looking at the quality of life in survivors of this disease [6,17,20]. The first study examined 132 patients over the age of 65 years who had aggressive NHL and received chemotherapy with cyclophosphamide, vincristine, doxorubicin, and prednisone (CHOP) [17]. Health-related quality of life was evaluated using the SF-36 and the Quality of Life Cancer Survivors questionnaire. At baseline, quality of life was significantly better on almost all dimensions in patients with a lower age-adjusted International Prognostic Index (IPI) [21] as compared with patients with a higher IPI. During treatment, physical and role functioning and global quality of life deteriorated and fatigue increased in the lower IPI group. Quality of life in those with a higher IPI remained stable. During follow-up, quality of life was significantly better for those patients with a complete or partial response to therapy. Finally, fatigue after therapy improved for those with a high IPI, and fatigue levels returned to baseline in those with a low IPI. Additionally, loss of appetite, changes in sleep patterns, and social functioning all improved after the completion of therapy.

In the second study, 294 patients with NHL (defined by International Statistical Classification of Diseases and Related Health Problems [ICD] 9 codes as lymphoma, not otherwise specified, lymphoma by diffuse histology, lymphosarcoma, or immunoproliferative disease) completed three surveys examining health-related quality of life [20]. These studies included the EuroQOL-5D, a generic instrument measuring five main dimensions in health, the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire, a cancer specific questionnaire focusing on function, and the Multidimensional Fatigue Inventory (MFI-20), a self-reporting instrument

on fatigue. Significantly worse psychological and social well-being and health-related quality of life were identified in patients who had received chemotherapy as opposed to those who had not received chemotherapy. Patients who were diagnosed 10–15 years earlier reported better social well-being than patients who were diagnosed 5–9 years earlier. Compared with age-matched controls, patients reported significantly worse general health and less vitality.

A third study more recently reported by Smith *et al.* evaluated quality of life in survivors of NHL of all subtypes [6], specifically looking at the quality of life in patients with active disease, as compared with short- and long-term survivors. As reported by Doorduijn *et al.* [17], individuals on active therapy reported more negative outcomes; however, the results in short- and long-term survivors were not significantly different.

In our study, we evaluated patients at least 1 year from the diagnosis of NHL, and specifically compared the results between those with indolent and aggressive NHL. We had hypothesized that patients with indolent NHL would have a poorer quality of life (QOL) compared to those with aggressive NHL. Patients with low grade or indolent NHL often require repeated courses of chemotherapy and immuno-therapy. They have been told by their physicians that they are generally not cured from their disease, and ultimately deal with the stress and consequences of knowing their disease will return. In contrast, those with aggressive NHL often have significant symptoms upon presentation and through chemotherapy, but they are generally cured and do not require repeated courses of multiple chemotherapy agents. Our results, however, did not support our hypothesis. Instead, they indicated no significant difference in quality of life between those with indolent and aggressive NHL. While this may be explained by the fact that 17% of our patients with indolent NHL had not required any therapy and 35% of them had stage I disease, even when the time from last treatment to survey was adjusted for using multivariate analysis, there was still no difference in the quality of life between the two groups. We also performed the analysis excluding patients who had never required therapy. In this analysis, there was no difference in overall QOL between the two groups.

Other groups have suggested that the largest decrease in quality of life scores is in young adults who receive therapy (25–34 years). In our study, the median age of our participants was 60 years. However, when adjusting for age, physical function was not more impaired in individuals with indolent NHL. Physical function, such as the ability to get out and walk and climb stairs, was more significantly impaired in individuals with aggressive NHL when compared with indolent NHL. Also, 94.8% of our patients with aggressive NHL had received chemotherapy; the use of chemotherapy has been shown by other groups to impair quality of life [20,22]. It is not clear from our data whether complications from chemotherapy such as neuropathy, cardiac dysfunction, or changes in weight, or some other variable, may have contributed to this decline in physical function. Additional groups have also suggested that survivors who have received therapy have greater problems with physical function, but regain normal mental health function [23]. With only 43.1% of our indolent group having received chemotherapy, the lack of active therapy in this group may explain why their physical function appeared significantly better than in those with aggressive NHL. Additionally, more research needs to be done on why survivors of

aggressive NHL have a decline in physical function. Finally, exercise after therapy has been shown to improve quality of life in survivors after active treatment. In our study, we did not evaluate the amount of exercise survivors were performing; it is possible that the unmeasured differences between these groups may explain the difference in physical function between those with indolent and aggressive NHL.

There are several limitations to our study. First, it is cross-sectional in design. As a result, we were not able to document changes in quality of life over time. Additionally, we are not able to make any conclusions regarding causal association between disease diagnosis, treatment, and quality of life and fatigue outcomes. Second, despite having a very good participation rate of 75%, this is a small study in which 109 subjects participated and 17% of the indolent group had not required any therapy. While other studies have demonstrated that patients on active therapy or having received chemotherapy have a lower self-reported quality of life, many of our patients had not required any therapy. As a result, this may have impacted our ability to truly assess the impact of having a chronic disease such as low grade NHL requiring intermittent therapy compared to those who have a curable disease and often never need treatment again. Even when the analysis was repeated excluding those who never had treatment, the findings were similar. Finally, we may not have had a large enough sample size to identify relevant differences in QOL between survivors with aggressive and those with indolent NHL.

Although our study may have been underpowered and, thus, unable to detect meaningful differences related to QOL, our results do suggest that physical function, such as walking and climbing stairs, in survivors of aggressive NHL is more impaired than in those with indolent NHL. The etiology of this decline in physical function, whether a result of aggressive chemotherapy or some other variable, should be explored. It is important that further research be performed in these areas, preferably with larger samples, to better understand the experience and needs of survivors with aggressive and indolent NHL.

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**Table I**

Patient characteristics and baseline demographics.

	All patients (n = 109)	Indolent (n = 51)	Aggressive (n = 58)	p-Value *
Age				0.1190
Mean ± SD	58.9 ± 14.1	61.1 ± 12.2	56.9 ± 15.4	
Sex				0.3977
Female	53 (48.6%)	27 (52.9%)	26 (44.8%)	
Male	56 (51.4%)	24 (47.1%)	32 (55.2%)	
PS at diagnosis				0.001 (Fisher's exact)
0	33 (30.3%)	24 (47.1%)	9 (15.5%)	
1	47 (43.1%)	17 (33.3%)	30 (51.7%)	
2	6 (5.5%)	1 (2.0%)	5 (8.6%)	
PS at survey				0.675 (Fisher's exact)
0	67 (61.5%)	34 (66.7%)	33 (56.9%)	
1	34 (31.2%)	15 (29.4%)	19 (32.8%)	
2	1 (0.9%)	0	1 (1.7%)	
Stage at diagnosis				0.9677
1	39 (35.8%)	18 (35.3%)	21 (36.2%)	
2	8 (7.3%)	4 (7.8%)	4 (6.9%)	
3	12 (11.0%)	5 (9.8%)	7 (12.1%)	
4	49 (45.0%)	24 (47.1%)	25 (43.1%)	
B symptoms				0.034 (Fisher's exact)
No	99 (90.8%)	50 (98.0%)	49 (84.5%)	
Yes	9 (8.3%)	1 (2.0%)	8 (13.8%)	
Remission status at survey				<0.0001
CR	81 (74.3%)	27 (52.9%)	54 (93.1%)	
PD	4 (3.7%)	3 (5.9%)	1 (1.7%)	
PR	3 (2.8%)	3 (5.9%)	0	
SD	21 (19.3%)	18 (35.3%)	3 (5.2%)	
Comorbidities				0.0010
0	55 (50.5%)	23 (45.1%)	32 (55.2%)	
1	15 (13.8%)	3 (5.9%)	12 (20.7%)	
2	35 (32.1%)	25 (49.0%)	10 (17.2%)	
3	2 (1.8%)	0	2 (3.4%)	
Autologous transplant				0.497 (Fisher's exact)
No	106 (97.2%)	51 (100.0%)	55 (94.8%)	
Yes	2 (1.8%)	0	2 (3.4%)	
Last therapy to survey				0.0050
1–2 years	31 (28.4%)	12 (23.5%)	19 (32.8%)	
2–5 years	8 (7.3%)	3 (5.9%)	5 (8.6%)	
<1 year	61 (56.0%)	27 (52.9%)	34 (58.6%)	
No therapy	9 (8.3%)	9 (17.6%)	0	

	All patients (n = 109)	Indolent (n = 51)	Aggressive (n = 58)	p-Value *
Diagnosis to first therapy				<0.001 (Fisher's exact)
1–2 years	3 (2.8%)	2 (3.9%)	1 (1.7%)	
2–5 years	1 (0.9%)	1 (2.0%)	0	
<1 year	91 (83.5%)	34 (66.7%)	57 (98.3%)	
No therapy	10 (9.2%)	10 (19.6%)	0	
Radiation				1.000 (Fisher's exact)
No	55 (50.5%)	26 (51.0%)	29 (50.0%)	
Yes	54 (49.5%)	25 (49.0%)	29 (50.0%)	
Surgery				0.621 (Fisher's exact)
No	105 (96.3%)	50 (98.0%)	55 (94.8%)	
Yes	4 (3.7%)	1 (2.0%)	3 (5.2%)	
Chemotherapy				<0.0001
No	32 (29.4%)	29 (56.9%)	3 (5.2%)	
Yes	77 (70.6%)	22 (43.1%)	55 (94.8%)	
Immunotherapy				<0.0001
No	49 (45.0%)	35 (68.6%)	14 (24.1%)	
Yes	60 (55.0%)	16 (31.4%)	44 (75.9%)	

PS, performance status; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

\* Two-sample *t*-tests were used to compare continuous variables;  $\chi^2$  or Fisher's exact test was used to compared categorical variables.

**Table II**Quality of life assessments<sup>\*</sup>.

	All groups (n = 109)	Indolent (n = 51)	Aggressive (n = 58)	p-Value <sup>†</sup>	p-Value <sup>‡</sup>
FACT-F	45.0 (8.0–52.0)	47.0 (13.0–52.0)	43.0 (8.0–52.0)	0.1181	0.5396
Mental Composite Score	54.2 (10.8–65.8)	54.6 (10.8–64.4)	53.3 (22.2–65.8)	0.2425	0.9043
Physical Composite Score	51.8 (11.2–66.5)	52.7 (25.0–66.5)	50.6 (11.2–61.7)	0.1955	0.1102
Social Function	56.8 (18.7–56.8)	56.8 (24.1–56.8)	51.4 (18.7–56.8)	0.1398	0.5632
Physical Function	52.8 (14.9–57.0)	54.9 (21.3–57.0)	51.0 (14.9–57.0)	0.0884	0.0479
Mental Health	52.8 (16.2–64.1)	55.6 (16.2–64.1)	50.0 (16.2–64.1)	0.2308	0.8228
Role Physical	52.0 (17.7–56.9)	56.9 (25.0–56.9)	49.5 (17.7–56.9)	0.0158	0.1244
General Health	47.2 (25.8–63.9)	47.2 (25.8–63.9)	47.2 (25.8–63.9)	0.5055	0.9613
Bodily Pain	55.4 (19.9–62.1)	55.4 (29.2–62.1)	55.4 (19.9–62.1)	0.3130	0.3375
Emotional Role	55.9 (17.0–55.9)	55.9 (17.0–55.9)	48.1 (17.0–55.9)	0.0246	0.6375
Vitality	55.2 (20.9–70.8)	55.2 (20.9–70.8)	54.8 (27.1–70.8)	0.3789	0.6723

FACT-F, Functional Assessment in Cancer Therapy – Fatigue.

<sup>\*</sup> Results given as median (min-max).<sup>†</sup> Wilcoxon rank-sum test or two-sample *t*-test on continuous variables.<sup>‡</sup> From multiple linear regression models, we adjusted for factors of age, time from last treatment to survey, use of chemotherapy, and number of comorbidities.