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Health-related quality of life in patients with indolent and aggressive non-Hodgkin lymphoma

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Abstract: Indolent and aggressive non-Hodgkin lymphomas (NHL) are common types of hematologic malignancies but their effect on quality of life (QoL) is understudied. In particular, the relation between different aspects of QoL and cognitive impairments and coping styles is relevant for individualized physical and mental health care. We studied emotional, physical, and subjective well-being in relation to cognitive capacities and coping style in 100 patients with NHL (44 females, age 61.3 ± 13.6). Questionnaires assessed health-related QoL (Functional Assessment of Cancer Therapy (FACT)), affect (Hospital Anxiety and Depression Scale, Positive and Negative Affective Schedule), distress (Distress Thermometer), and locus of control; semi-structured interviews targeted subjective QoL (Schedule for Evaluating the Individual Quality of Life) and cognitive impairments (Test for Early Detection of Dementia with Differentiation from Depression). Indolent NHL ($n = 44$) yielded better health-related QoL and positive affect and less anxiety than the aggressive type ($n = 55$; FACT: $t(97) = 1.90, p = .028$, anxiety: $t(97) = -1.9, p = .030$; positive affect: $t(96) = 2.01, p = .023$). In a factor analysis, physical and affective scales loaded on an emotional and physical well-being factor, which differed between the groups. Further, cognitive capacities and locus of control contributed to subjective QoL and reported distress. Emotional and physical scales assess QoL in NHL. However,

ABOUT THE AUTHORS

The behavioral psychobiology group of the RWTH Aachen University seeks to unravel systemic biological factors underlying and influencing human well-being. The principal method is functional imaging in addition to psychometric approaches. Psychosomatic effects on emotions and cognitions are studied as well as regulation strategies to improve well-being using behavioral, pharmacological, and neurofeedback approaches.

PUBLIC INTEREST STATEMENT

Non-Hodgkin lymphoma (NHL) is the most common blood cancer. The indolent and aggressive subtypes differ in survival time and treatment options but little of their impacts on quality of life (QoL) is known. Physical, affective, and cognitive factors influence QoL in cancer. In 100 NHL patients, we measured emotional, physical, and subjective well-being as well as cognitive capacities and coping style. Physical and emotional well-being was higher in the group with indolent cancer. In a factor analysis, the measures of physical well-being, depression, anxiety, and affect loaded on one main factor, which clearly differed between the groups. However, other factors suggested an influence of coping strategies and cognitive abilities on other QoL instruments, in particular subjective QoL and distress. Psychophysical QoL appears a valid construct in NHL, but coping strategies influence subjective evaluation and help-seeking behavior, which may be hampered in patients with cognitive impairments.

cognitive impairments or external locus of control may hamper reporting of distress. Psychosocial support should specifically target at-risk patients.

Subjects: Anxiety & Mood Disorders; Anxiety in Adults; Behavioral Medicine; Hematologic Oncology; Mood Disorders in Adults - Depression, Mania, Bi-polar; Quality of Life

Keywords: psychooncology; cancer; locus of control; coping

1. Introduction

Non-Hodgkin lymphoma (NHL) is the sixth most common form of cancer, accounting for about 4% of all malignancies (Howlader et al., 2014). With respect to clinical outcome and impact on the patients, NHL can broadly be classified into two groups, indolent and aggressive lymphomas (Evans & Hancock, 2003). Generally, indolent lymphomas grow slowly, are often long asymptomatic; but the therapy is difficult and in the advanced stages, they are usually not curable. The faster growing aggressive lymphomas have poor survival outcome when not treated, but a rapid systemic chemotherapy in conjunction with antibodies such as rituximab can be curative (Shankland, Armitage, & Hancock, 2012). Such aggressive immune-chemotherapeutic regimes, however, can often produce significant acute and chronic adverse effects, with significant impact on the patients' well-being (Bellizzi et al., 2009).

The incidence of NHL is increasing worldwide, but also the survival has improved substantially, reaching about 69% (Howlader et al., 2014). The longer survival can be attributed to two factors: improved treatment regimens and a slower tumor growth in the aging population (Shankland et al., 2012). Consequently, an increasing number of NHL survivors, reaching in the United States over half a million, have to deal with the long-term and late effects of this chronic disease (Howlader et al., 2014; Naughton & Weaver, 2014). This includes not only the lymphoma-specific symptoms such as fever, night sweats, and weight loss, but also co-occurring emotional distress, which can be challenging for the patients and diminish their quality of life (QoL; for a review see Leak, Mayer, & Smith, 2011).

In addition to survival times, health-related QoL has become a widely accepted outcome measure in cancer research, constituting one of the most important treatment goals (Wedding, Pientka, & Höffken, 2007). It is a multi-dimensional construct influenced by physical functioning (e.g. fatigue and/or pain), mental health (e.g. anxiety and/or depression), cognitive abilities, and social factors (Naughton & Weaver, 2014). While many studies addressed QoL in breast, prostate, colorectal, and lung cancer, NHL is an understudied patient group (Kent et al., 2015; Smith et al., 2013).

The first systematic review of QoL in Hodgkin and NHL demonstrated worse physical but comparable mental QoL in patients as compared to the general population (Arden-Close, Pacey, & Eiser, 2010). Two studies demonstrated lower general health and more problems with work and finances as well as higher rates of anxiety and depression in NHL survivors compared to their peers in the general population (Jensen et al., 2013; Mols et al., 2007). Moreover, active treatment was associated with impaired physical functioning and worse psychological and social well-being (Mols et al., 2007; Smith, Zimmerman, Williams, & Zebrack, 2009).

Although the research of QoL in NHL survivors is growing, the heterogeneity of this disease is rarely taken into account. Studies focused mostly on QoL associations with socio-demographic and clinical characteristics, while limited research has been dedicated to the impact of differing clinical characteristics of aggressive and indolent forms on patients' well-being (Jensen et al., 2013). QoL has been studied in indolent (Webster & Cella, 1998) and aggressive forms of NHL (Doorduijn et al., 2005; Jensen et al., 2013) but, to our knowledge, only one study made a direct comparison so far, finding no differences except for better physical function within the indolent patient group (Blaes, Ma, Zhang, & Peterson, 2011).

In addition to biological factors, cognitive variables such as control beliefs are important predictors for the adjustments to chronic disorders. For instance, in other types of cancer, locus of control is the most frequently assessed control beliefs (see review in Neipp, Lopez-Roig, & Pastor, 2007). Indeed, locus of control is associated with QoL in hematological cancer as well (Allart, Soubeyran, & Cousson-Gélie, 2013). Further, cognitive impairments may interfere with reappraisal and thus reduce QoL (Sarkheil et al., 2014). In a sample of cancer patients after whole-brain radiation therapy, cognitive impairments predicted a decrease of QoL over time (Li, Bentzen, Li, Renschler, & Mehta, 2008). Conceivably, cognitive factors such as control beliefs (locus of control) and cognitive functions (impairments and intelligence) may contribute to QoL in NHL.

To better understand factors influencing QoL in NHL, we examined multi-dimensional QoL in 100 patients with aggressive and indolent forms of NHL. We applied selected scales, based on the existing literature on NHL, to assess cancer—as well as lymphoma-specific QoL, emotional and cognitive functions, subjectively valued QoL, and physical functions. Patients with the aggressive form of NHL were hypothesized to demonstrate lower health-related QoL as well as higher depression and anxiety than those with the indolent form. Exploratory analyses of differences in cognitive strategies of coping with the chronic disease should shed light on the factors underlying the different measures for QoL in NHL.

2. Methods

2.1. Participants

One hundred patients with NHL were recruited from the in and outpatient services of the Department of Oncology, Hematology, Hemostaseology and Stem Cell Transplantation at the University Hospital Aachen. The patients age ranged from 23 to 85 years ($M = 61.32$, $SD = 13.6$, 44 females; for demographics and basic clinical data see Tables 1 and 2). One patient withdrew informed consent and was excluded from the analysis. No exclusion criteria were applied. All participants were right-handed, fluent German speakers, and gave written informed consent before participation. Inclusion criteria were the histological diagnosis of a NHL according to the 2008 WHO classification (Swerdlow et al., 2008). Eligible patients were asked by the treating physician whether they might be interested in participating in a study on QoL in NHL patients and if they agree to be contacted by the study personal. Based on the WHO classification of lymphoma, the patients were classified into either an indolent (low grade B-cell or T-cell NHL; $n = 46$) or an aggressive NHL group (high or intermediate grade B-cell or T-cell NHL; $n = 53$). The Ethics Committee of the Medical Faculty of the RWTH Aachen University, Germany, approved the study protocol (EK123/11) in accordance to the Declaration of Helsinki.

2.2. Procedure

After being contacted by the treating physician, a trained rater explained the study procedure and aims to the patients. After the agreement to participate in the study, an appointment was made. The testing took place in the patient's room or the doctor's office of the outpatient services without other persons present except the rater and the patient. Standard instructions for each questionnaire and its items were read out loud to each patient. The participants could choose whether either they marked their response themselves or had the examiner do it for them. Two of the questionnaires—the Schedule for Evaluating the Individual Quality of Life (SeiQoL) as a semi-structured interview and the Test for Early Detection of Dementia with Differentiation from Depression (TFDD)—were always completed by the examiner. At the end of the testing session, a debriefing took place ensuring that the patient was feeling well, after discussing sensitive issues of their personal experiences. The testing session lasted about 60–90 min depending on the pace of the patient and their comprehension of the questions and tasks. It took place in the clinical environment without any other person present in the room. The order of the questionnaires were randomized and balanced. The patients received compensation for their time in the amount of 10€ per hour. Further, the treating physicians provided information about demographics such as age, gender, education, and about the clinical status and medical history by filling in a basic documentation (Knight et al., 2015).

Table 1. Socio-demographic information for indolent and aggressive NHL groups

	All patients (n = 99)	Indolent NHL (n = 46)	Aggressive NHL (n = 53)	Group comparison
	n (%)	n (%)	n (%)	p-value*
Gender				.106
Male	56 (56.6)	30 (65.2)	26 (49.1)	
Female	43 (43.4)	16 (34.8)	27 (50.9)	
Education				.910
Hauptschule (secondary general school)	20 (20.2)	9 (19.6)	11 (20.8)	
Realschule (sec- ondary school)	17 (17.2)	7 (15.2)	10 (18.9)	
Gymnasium (high school)	29 (29.3)	14 (30.4)	15 (28.3)	
Other school	31 (31.3)	16 (34.8)	15 (28.3)	
Steady relationship				.667
Yes	83 (83.8)	39 (84.8)	44 (83.0)	
No	12 (12.1)	6 (13.0)	6 (11.3)	
Unknown	4 (4.0)	1 (2.2)	3 (5.7)	
Children				.968
Yes	76 (76.8)	36 (78.3)	40 (75.5)	
No	9 (9.1)	3 (6.5)	6 (11.3)	
Unknown	14 (14.1)	7 (15.2)	7 (13.2)	
Employment status				.402
Employed	14 (14.1)	7 (15.2)	7 (13.2)	
Sick leave	33 (33.3)	13 (28.3)	20 (37.7)	
Retired	49 (49.5)	25 (54.3)	24 (45.3)	
Home duties	1 (1.0)	1 (2.2)	0 (.0)	
Other	2 (2.0)	0 (.0)	2 (3.8)	

*Statistics with χ^2 or two-sample *t*-tests.

2.3. Measures

We applied a battery of instruments to assess patients' emotional, social, cognitive, and physical functions in a multi-dimensional fashion. Three instruments assessed QoL directly as a construct: Functional Assessment of Cancer Therapy: General (FACT-G; second version), Functional Assessment of Cancer Therapy: Lymphoma (FACT-Lym), and SeiQoL:

The FACT-G (second version) is a cancer-specific instrument investigating the health-related QoL in four domains: physical, social/family, emotional, and functional well-being (Cella et al., 1993). It was generated in several steps: first, items were generated based on semi-structured interviews with patients and oncology specialists; items were reduced before finally the scale was constructed. These items are presented on the scale as statements which are rated by the participants on a Likert scale from 0 (not at all) to 4 (very much) indicating how true it has been in the past week. The responses are summed up, with reverse coding for negative items, so that a high score indicates a better health-related QoL. As an example item, the first statement on the subscale physical well-being is "I have a lack of energy"; another example item from the subscale social/family well-being is "My family has accepted my illness". The FACT-G has a high test-retest of .92 as measured in 60 outpatients with cancer diagnoses. In our sample, Cronbach's α measured reliability of the total score and the subscales between .75 and .89 (6–7 or 20 items, $n = 97–99$). There is evidence for high

convergent validity by comparing it to similar measures such as the Functional Living Index-Cancer (FLIC; $r = .79$) and to measures of mood such as the Profile of Mood States-Brief (briefPOMS; $r = .68$). A high divergent validity was confirmed by low correlations between the FACT-G and measures of social desirability as the Marlowe Crowne Social Desirability Scale (M-CSDS; $r = .22$; Cella et al., 1993).

The instrument FACT-Lym (Hlubocky, Webster, Cashy, Beaumont, & Cella, 2013) complements the FACT-G with a list of symptoms specific for lymphoma. It was also developed in three steps: item generation, item reduction, and construction of the measurement. A high score on this scale also indicates a higher health-related QoL. An example of its 15 statements is “I am bothered by lumps or swelling in certain parts of my body (e.g. neck, armpits, or groin)”. A good internal consistency reliability was proven at three time points ($T1 = .79$, $T2 = .85$, and $T3 = .84$) and with a test-retest correlation coefficient of $r = .84$. In our sample, Cronbach’s α measured reliability as .89 (15 items, $n = 94$). Convergent validity was tested comparing the FACT-Lym to validated measures such as the Physical Component Summary (PCS) and the Profile of Moods States Fatigue subscale (POMS-F), each with $r = .62$ ($p = .0001$). A high divergent validity was confirmed by low correlations between the FACT-Lym and the M-CSDS ($r = -.15$; Hlubocky et al., 2013).

The SeiQoL (O’Boyle, Browne, Hickey, McGee, & Joyce, 1993) is a semi-structured interview exploring individual QoL for subjective areas of values and to subsequently quantify them in a weighted sum score (Waldron, O’Boyle, Kearney, Moriarty, & Carney, 1999). The participants freely named their five most important areas in life, which were labeled as “cues”. Then, for each of these cues, the current status was rated on a visual analog scale from 0 to 100. Further, a weighting of the relevance for each cue was determined, enabling the calculation of an all-over SeiQoL index as weighted mean (range: 0–100). Patel, Veenstra, and Patrick (2003) reviewed studies comparing the reliability and validity of different instruments designed to measure individual health-related quality of life. The SeiQoL had adequate test-retest reliability with $r = .88$. In contrast to the Patient-Generated Index (PGI), SeiQoL showed a high internal reliability ranging from $r = .6$ to $.9$ and a high content validity $r = .72-.88$.

Two instruments assessed emotional state and distress:

The Hospital Anxiety and Depression Scale (HADS; Zigmond & Snaith, 1983) is a self-assessment two-dimensional scale reflecting the current state of depression and anxiety of patients in a hospitalized setting. It was validated—among others—in cancer populations and has good psychometric properties (Annunziata, Muzzatti, & Altoe, 2011). A study by Helvik, Engedal, Skancke, and Selbæk (2011) found an internal consistency reliability of .82 for the complete scale as well as .79 and .78 for the subscales, anxiety and depression, respectively. In our sample, Cronbach’s α measured reliability as .81 and .83 (7 items, $n = 98$). The concurrent validity of .6 ($p < .01$) resulted from comparing the HADS to the emotional items of the Montgomery–Aasberg depression rating scale (MADRS). The authors concluded that the HADS distinguishes well between depression and anxiety and it can be used with medically hospitalized elderly.

The Distress Thermometer is a single visual analog scale, which was developed by the National Comprehensive Cancer Network (2003) to measure the psychosocial distress in patient groups. The patients indicate the level of distress they have experienced over the past week on a visual scale (range: 0–10), where 0 indicates no distress, 5 moderate distress, and 10 extreme distress. A review by Donovan, Grassi, McGinty, and Jacobsen (2014) assessed the sensitivity of the instrument in a group of prostate cancer patients, compared it to the HADS, and evaluated its validity over 12 months using ROC analysis to identify cut-off values. The Distress Thermometer was found to be sensitive against the anxiety and depression subscales of the HADS with AUCs of .84 (95% CI = .78–.90) and .82 (95% CI = .68–.97) and the AUC to the total HADS of .83 (95% CI = .77–.90) using a cut-off of ≥ 3 . A cut-off of ≥ 4 was shown to remain fairly sensitive after 12 months for the subscale depression (AUC = .73, 95%-CI = .58–.87) and the total HADS (AUC = .80,

95%-CI = .70-.89); the cut-off score of ≥ 6 applied to the subscale anxiety (AUC = .83, 95%-CI .73-.93). Their review confirmed its validity to identify distress, anxiety, and depression in a cancer population.

The Positive and Negative Affective Schedule (PANAS; Watson, Clark, & Tellegen, 1988) measures positive and negative mood. This instrument includes a list of 20 adjectives and a five-point Likert scale to indicate the experienced status of each adjective over a specific period. The two independent outcome variables—positive affect and negative affect—are calculated by summing up the 10 items on each subscale. Positive affect relates to enthusiasm, alertness, and the level of activity; the higher the score, the higher the person's energy. A high score on the negative affect subscale reflects distress and aversive mood state, whereas a low score indicates calmness and serenity. Its reliability was tested for different time instructions, such as “today” and “in the past few weeks”. The internal consistency reliabilities are high for the positive affect as well as for the negative affect subscale, ranging from .86 to .90 and from .84 to .87, respectively. In our sample, Cronbach's α measured reliability as .86 and .88 (10 items, $n = 91$). The comparison of the two subscales confirmed a high divergent validity with low correlations ranging from $r = -.12$ to $-.23$, depending on the time of instruction (Watson et al., 1988).

Three more instruments quantified cognitive strategies and resources:

The standardized German instrument to health locus of control (KKG, Kontrollüberzeugungen zu Krankheit und Gesundheit) is operationalized with three outcome variables of control beliefs: internality, externality powerful others (POs), and externality chance (Lohaus & Schmitt, 1989). Internal control is high if patients believe their own behavior and their own personality are the source of their health control. The remaining variables reflect the belief that external sources have control over patient, i.e. someone else, e.g. a doctor (POs) or fortune/luck (chance). The internal consistency reliability for the subscales ranges from $r = .66$ to $.76$, and their test-retest reliability between $r = .72$ and $.77$ (Lohaus & Schmitt, 1989). In our sample, Cronbach's α measured reliability as .77, .62, and .72 (7 items, $n = 92$). The internal dimension and the external ones (POs and chance) are independent (Luszczynska & Schwarzer, 2005).

The German multiple selection vocabulary test (MSVT-B; Merz, Lehr, Galster, & Erzigkeit, 1975) characterizes premorbid verbal intelligence. It consists of a list with five words in each line; out of these five words, only one is found in a dictionary and the others are imaginary. The task is to identify the correct word. An example could be “nesa - naso - nose - neso - nosa”. The review by Lehl, Triebig, and Fischer (1995) finds a fair convergent validity between the MSVT-B and different IQ tests (median $r = .72$ in 22 samples), with the highest correlation of $r = .81$ in comparison to the WAIS-Full-IQ.

The TFDD (Ihl et al., 2000) detects early dementia symptoms and attempts to differentiate them from depression. The questions address immediate and delayed memory functions, praxis, verbal fluency, and orientation in time and space. The outcome score for cognitive impairments ranges from 0 to 50. A cut-off value of < 35 indicates a case of dementia. A separate score averages the level of depression from a self- and a rater-scale. A cut-off of > 8 refers to depression. A high inter-rater reliability of $r = .99$ ($p < .001$) was found for the dementia symptoms; for the depression symptoms $r = .75$ ($p < .001$). The test-retest reliability was $r = .87$ ($p < .001$) for the dementia items and $r = .70$ ($p < .05$) for the depression items. There is evidence for high convergent validity of the dementia items compared to similar measures such as the Mini-mental-status-test (MMST; $r = -.84$, $p < .001$), the cognitive subscale of the Alzheimer's disease assessment scale (ADAS; $r = -.89$, $p < .001$), and the sum score of the short cognitive performance test ($r = .86$, $p < .001$; Ihl et al., 2000).

2.4. Statistical analyses

Demographic information and test scores were compared between the groups (indolent vs. aggressive) using two-sample t -tests for continuous variables and χ^2 tests for categorical data. Factor

analysis investigated the data structure. Therefore, a principal component analysis (PCA) was conducted on all 14 outcome scores of the questionnaires. Only factors with eigenvalues of at least 1 were considered. A high intercorrelation between the scales was expected and thus no factor rotation performed. Factor loadings of .4 and higher reflected relevant contribution from the respective test score. Factor scores were compared between the groups in two-sample *t*-tests. All statistical analyses were performed with SPSS 20 for Windows (SPSS Inc., Chicago, USA); the level of significance was set at $p = .05$ for the hypothesized direction.

3. Results

3.1. Demographic information

There were no significant differences between the groups concerning age, demographic data, disease duration, or clinical status (see Tables 1 and 2). We expected the diagnosis to influence the clinical treatment. In particular, a significant relationship between chemotherapeutic treatment and the malignancy of the lymphoma emerged ($\chi^2(1) = 6.22, p < .006$), with higher rate of chemotherapy in the aggressive subgroup. In a similar vein, a significant association was found between radiation therapy and the NHL type ($\chi^2(1) = 4.80, p < .014$) due to the use of radiation therapy in the indolent subgroup only. In 77.8% of the sample, other relevant physical diseases were recorded; 12.1% were currently given psychoactive medications/opiates and 4% of the patients had previous psychological or psychiatric treatments.

3.2. Group comparison of scales

The indolent group demonstrated significantly higher quality of life as measured with FACT-G ($M = 78.85, SE = 2.43$) than the aggressive group ($M = 72.34, SE = 2.33; t(97) = 1.93, p = .028$). The disease-specific FACT-Lym scale did not differ significantly between the indolent ($M = 43.93, SE = 1.41$) and the aggressive groups ($M = 41.05, SE = 1.44; t(97) = 1.41, p > .2$; Figure 1(a)). No significant difference emerged for the SeiQoL index between the indolent ($M = 73.01, SE = 2.1$) and the aggressive NHL groups ($M = 71.05, SE = 2.47; t(95) = .59, p > .2$).

Concerning the affective symptoms on the HADS, patients with indolent NHL reported significantly less anxiety ($M = 4.46, SE = .49$) than patients with aggressive NHL ($M = 5.91, SE = .57; t(97) = -1.89, p = .03$). No difference between the groups was found in the HADS depression scores between patients with indolent NHL ($M = 4.57, SE = .64$) and those with aggressive NHL ($M = 5.64, SE = .59; t(97) = -.55, p = .112$; Figure 1(b)). Further, the Distress Thermometer failed to document differences between the two groups ($t(96) = -.98, p = .160$). In regard to mood ratings on the PANAS, positive affect was higher in the indolent ($M = 33.85, SE = 1.06$) than in the aggressive lymphoma group ($M = 30.58, SE = 1.20; t(96) = 2.01, p = .023$; Figure 1(c)). Negative affect did not differ between the indolent ($M = 18.46, SE = .92$) and aggressive lymphoma groups ($M = 19.65, SE = 1.12; t(96) = -.60, p > .2$).

No difference was found for the locus of control between the groups on any of the three subscales of the KKG: internality ($t(96) = -.23, p > .2$), externality powerful others ($t(96) = -.27, p > .2$), and externality chance ($t(96) = .09, p > .2$). Further, patients with indolent NHL did not differ in the TFDD dementia score ($M = 42.18, SE = .73$) from patients with aggressive NHL ($M = 41.98, SE = .81; t(92) = .18, p > .2$). Finally, no difference emerged on the depression scale of the TFDD between the indolent ($M = 5.54, SE = .53$) and the aggressive groups ($M = 5.88, SE = .54; t(92) = -.84, p > .2$).

3.3. Factor analysis

A factor analysis without rotation was conducted on the 14 outcome scores of the applied instruments. The Kaiser–Meyer–Olkin score was .75 indicating satisfactory sample size (84 subjects completed all scales; in the others, one or more was missing mostly due to exhaustion over the course of the interview) (Kaiser, 1974). The Bartlett's test for sphericity was significant ($\chi^2(91) = 451.07, p < .001$) implying that the variables correlated with each other. Four components yielded eigenvalues of at least 1.0 and explained 64.7% of variance in total. The other factors were not considered. Table 3 lists the factor loadings of each variable. Based on this factor structure, the factors were

Table 2. Clinical information for indolent and aggressive NHL groups

	All patients (n = 99)	Indolent NHL (n = 46)	Aggressive NHL (n = 53)	Group comparison
	n (%)	n (%)	n (%)	p-value
Current NHL status				.339
First illness	72 (72.7)	30 (65.2)	42 (79.2)	
Second tumor	1 (1.0)	1 (2.2)	0 (.0)	
Recurrence/Progression	20 (20.2)	12 (26.1)	8 (15.1)	
Remission	5 (5.1)	3 (6.5)	2 (3.8)	
Unknown	1 (1.0)	0 (.0)	1 (1.9)	
Treatments				
Operation	11 (11.1)	5 (10.9)	6 (11.3)	
Chemotherapy	88 (88.9)	37 (80.4)	51 (96.2)	
Radiation	4 (4.0)	4 (8.7)	0 (.0)	
Stem cell transplantation	9 (9.1)	6 (13.0)	3 (5.7)	
Other	6 (6.1)	4 (8.7)	2 (3.8)	
Other physical diseases				.914
Yes	77 (77.8)	36 (78.3)	41 (77.4)	
No	22 (22.2)	10 (21.7)	12 (22.6)	
Psychoactive medication/opiates				.291
Yes	12 (12.1)	6 (13.0)	6 (11.3)	
No	85 (85.9)	44 (95.7)	41 (77.4)	
Unknown	2 (2.0)	2 (4.3)	0 (.0)	
Previous psychological treatment				.64
Yes	4 (4.0)	2 (4.3)	2 (3.8)	
No	94 (94.9)	44 (95.7)	50 (94.3)	
Unknown	1 (1.0)	0 (.0)	1 (1.9)	
Current level of functioning (ECOG)				.818
Normal activity	22 (22.2)	10 (21.7)	12 (22.6)	
Symptoms, but nearly fully ambulatory	55 (55.6)	29 (63.0)	26 (49.1)	
Some bed time, but needs to be in bed less than 50% of the waking hours	14 (14.1)	8 (17.4)	6 (11.3)	
Needs to be in bed more than 50% of normal waking hours	8 (8.1)	5 (10.9)	3 (5.7)	

labeled “emotional and physical wellbeing”, “cognitive capacities”, “dependence on others”, and “help-seeking”.

The factor emotional and physical well-being explained 32.3% of variance with positive correlation with the QoL questionnaires and positive affect and negative association with anxiety,

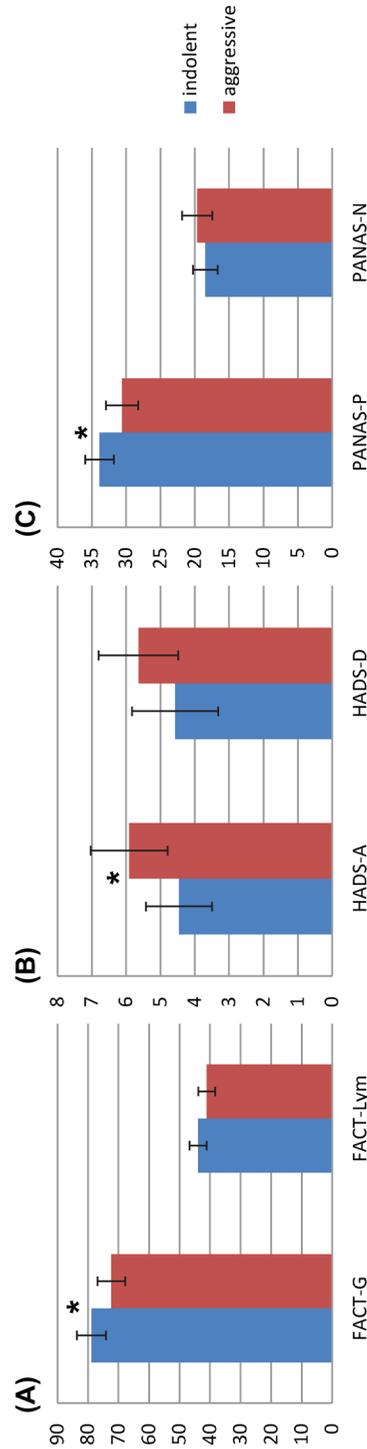


Figure 1. Group comparison (indolent vs. aggressive NHL) of quality of life.

Notes: The panels represent FACT-G and FACT-Lym (A), HADS (B), and PANAS (C); bar plots of group mean with 95% confidence interval. The general FACT scale, anxiety, and positive affect were significantly better in the indolent as compared to the aggressive NHL group (*: $p < .05$).

Table 3. Principal component analysis of the QoL-related outcome variables

	Factor loadings			
	Emotional and physical well-being	Cognitive capacities	Dependence on others	Help-seeking
FACT-G	.818	.225	.056	-.126
FACT-LYM	.752	.145	.179	-.030
SeiQoL index	.457	-.406	.107	-.201
Anxiety (HADS)	-.810	.170	.149	-.178
Depression (HADS)	-.813	-.318	.092	.026
Distress Thermometer	-.554	-.016	-.327	.496
Negative affect (PANAS)	-.722	.157	-.008	-.190
Positive affect (PANAS)	.560	.417	-.140	.143
Internal LOC (KKG)	-.105	.668	.140	.535
Powerful others LOC (KKG)	-.132	.566	.416	-.455
Chance LOC (KKG)	-.174	.536	.529	.177
MWT-B (verbal intelligence)	-.110	.513	-.535	-.205
Cognitive performance (TFDD)	-.014	.427	-.655	-.249
Depression (TFDD)	-.746	.075	.063	-.204
Eigenvalues	4.53	2.06	1.39	1.06
% of variance	32.4	14.8	10.0	7.6

Note: Factor loadings with contributions larger than .4 are set in bold.

depression, and negative affect. Cognitive capacities explained 14.8% of the variance and predicted higher cognitive scores and positive affect, whereas the SeiQoL was negatively correlated. Dependence on others explained 10.0% of the variance reflecting higher external control scores (POs, chance) and lower intelligence (verbal intelligence and TFDD score). Low verbal IQ and cognitive impairments seem to result in attribution of external factors to control. The factor help-seeking explained 7.6% of the variance; high internal LOC and low POs seem to lead to higher ratings on the visual analog scale for distress.

Only the first factor scores between the groups yielded significant difference between the groups, i.e. emotional and physical well-being was significantly higher in the indolent ($M = .21, SE = .14$) as compared to the aggressive group ($M = -.20, SE = .15; t(82) = -1.98, p = .025$). The higher well-being in the indolent group was mainly reflected by a better mood and a lower symptom load. The other three factors failed to show a significant difference between the groups (cognitive capacities: $t(82) = .52, p = .301$, dependence on others: $t(82) = .31, p > .2$, and help-seeking: $t(82) = .02, p > .2$).

4. Discussion

In line with our hypothesis, patients with the aggressive form of NHL demonstrated a somewhat lower QoL, including physical, social/family, emotional, and functional well-being, as well as higher anxiety and lower positive affect than patients with indolent NHL. The group difference was, however, rather small. The factor analysis revealed four main components contributing to patients' functioning: emotional and physical well-being, cognitive capacities, dependence on others, and help-seeking. Coping styles and cognitive capacity seem to influence the subjective evaluation and the reporting of QoL and distress.

One previous study compared the QoL in patients with aggressive and indolent NHL but found no differences between the groups (Blaes et al., 2011). Similarly, we found no differences between NHL groups using the more general SeiQoL measure, but did find a difference using the FACT-G measure. This lack of differences might depend on the choice of questionnaires: the study applied a generic QoL scale and a fatigue scale. A number of studies support the use of disease-specific scales rather than generic ones to assess the subtle differences within the patient population since they are more sensitive to detect certain aspects of the disease and treatment that are relevant to a specific patient group (Mathiak, Mathiak, Karzel, Wola, & Ostaszewski, 2010; Oerlemans, Mols, & Nijziel, 2011). We found, however, no differences between the groups on the lymphoma-specific scale (FACT-Lym). The FACT-Lym assesses, in fact, the clinical symptomatic characteristic for lymphoma; the lack of differences on this scale confirms that both groups were similar with respect to their clinical status.

Significant differences between indolent and aggressive NHL groups emerged for anxiety (HADS) and positive affect (PANAS) but not for depression, negative affect, or cognitive measures. Aggressive NHL may acutely deter health or lead to death; therefore, this subtype may directly induce anxiety. In a similar vein, positive affect has been suggested to reflect rather interoceptive mechanisms and emotions directly in contrast to negative affect being influenced by cognitive processing (Mathiak, Klasen, Zvyagintsev, Weber, & Mathiak, 2013). Thus, the lack of significant group differences for negative affect (PANAS), depression (HADS and TFDD), and distress (Distress Thermometer) may reflect that the latter factors are influenced by cognitive processes such as coping (see Chiou, Potempa, & Buschmann, 1997). Cognitive functions such as locus of control (KKG), cognitive impairments (TFDD), and verbal intelligence (MWT-B) did not differ between the groups. Depression and positive affect may be directly affected by the disease process and cognitive processes may influence the other affective measures leading to a lack of group differences in addition to unsystematic effects.

Four components were identified within a factor analysis conducted with the above-mentioned measures. In summary, physical and affective scales loaded on an emotional and physical well-being factor, which differed between the groups. Within the remaining factors, associations between cognitive impairments, LOC, QoL, and distress were identified. Cognitive impairments and external locus of control may hamper NHL patients' reporting of distress.

Factor emotional and physical well-being: The applied factor analysis has to be treated as explorative method but it confirmed the discriminative profile of the *t*-tests and segregated the scales in a meaningful way. A high collinearity between QoL measures must be expected and thus the first factor should have particular high relevance. The first factor, accordingly, reflected general QoL and a third of the variance of the data. In this factor, very high loadings emerged for both scales each in FACT, HADS, and PANAS as well as for the TFDD depression scale. The observation that this factor differed between the indolent and the aggressive groups is an indicative that the disease-related psycho-physical distress mostly maps on one general QoL dimension.

Factor cognitive capacities: Cognitive coping strategies and adaptation mechanisms seem to influence aspects of QoL independent from disease factors. In our study, subjective QoL, the Distress Thermometer, and positive affect from the PANAS exhibited a somewhat smaller loading on the general QoL factor but showed relevant contributions to the other factors. In particular, the latter measure and health-related locus of control loaded on cognitive impairments and health-related locus of control. Higher cognitive capacities may enhance cognitive reappraisal and thereby increase positive affect (Sarkheil et al., 2014). Such search for coping strategies, however, may interfere with subjective QoL since different cues (life areas and values) contribute to the global SeiQoL scale.

Factor dependence on others: Cognitive impairments were associated with higher external locus of control. Thus, patients with reduced intellectual abilities may be at risk of developing dependent behavior and reduced functional status (see Repetto et al., 2002). Indeed, cognitive impairments predicted lower QoL in patients after whole-brain radiation (Li et al., 2008). Notably, hematological disorders may directly lead to cognitive impairments and thereby reduce QoL (Meyers, Albitar, & Estey, 2005).

Factor help-seeking: Locus of control and coping strategies are associated with QoL in hematological cancer (see review in Allart et al., 2013). In our factor analysis, patients with high internal and low external (powerful others) locus of control were more likely to indicate the wish for support in the Distress Thermometer. Indeed, help-seeking behavior is known to be influenced by the expected benefit (Ryan & Pintrich, 1997) and, thus, may be associated with an active coping style as observed with internal locus of control (Petrosky & Birkimer, 1991). Interestingly, the latter three factors involving cognitive capacities and styles did not differ between patients with indolent and aggressive NHL and, thus, may act as an independent factor on QoL. In general, a direct coping style was associated with internal locus of control, predicting more direct coping (Petrosky & Birkimer, 1991), better treatment outcomes, e.g. in lower back pain (Härköpää, Järvikoski, Mellin, Hurri, & Luoma, 1991) or aggressive NHL (Jensen et al., 2013), and can be associated with more active help-seeking. In our NHL group, internal rather than external locus of control was associated with help-seeking and higher reported distress on the Distress Thermometer. In line with a previous study (Broers, Kaptein, Le Cessie, Fibbe, & Hengeveld, 2000), the group with external locus of control may be particularly accessible to support, despite the less active coping style and personalized pharmacological treatment of impaired mood may be considered (Laoutidis & Mathiak, 2013).

4.1. Implications for clinical practice and research

FACT-G and HADS are well-established instruments to study QoL and well-being in cancer patients (Annunziata et al., 2011; Cella et al., 1993; Helvik et al., 2011). Our data confirmed that these instruments are also well-suited to assess psycho-physical well-being in NHL patients. Interestingly, the physical-dominated measures in the FACT-G and the mood measures in the HADS loaded on the same factor, suggesting a high interdependence of affective state and physical well-being in this patient group. The HADS may be the most widely applied screening tool in oncology to detect distress (Mehnert, Lehmann, Cao, & Koch, 2006) and it can be assumed to capture significant contributions to psycho-physical well-being. In a similar vein, the Distress Thermometer has been developed as one-dimensional indicator for distress (National Comprehensive Cancer, 2003); however, in our sample, the reported distress seems to be influenced significantly by cognitive factors as well. For instance, patients with reduced intellectual abilities may be at risk of developing dependent behavior and should be provided with support for coping, to improve the functional status (Extermann & Hurria, 2007; Repetto et al., 2002; Rodin & Mohile, 2007). We suggest that screening instruments for distress in hematological cancer—in particular, the Distress Thermometer—should be better evaluated for their efficacy rather than only their psychometric properties.

A previous study suggested that the SeiQoL does not only measure QoL but reflects other cognitive factors as well (Moons, Marquet, Budts, & De Geest, 2004). In our study, the factor cognitive capacities showed a similar loading as the main emotional and physical well-being factor. Indeed, the SeiQoL test procedure may be too complex for the cognitively impaired (Moons et al., 2004). Additionally, this relation may reflect a lesser adaptive capacity to develop effective coping strategies. Moons et al. (2005) suggested that QoL research should rather focus on wants rather than needs. The SeiQoL may be a suitable instrument to extend the view on patients' values and personalize the treatment targets.

4.2. Limitations

Recruitment at a center for specialized care may have led to an overrepresentation of acutely sick patients with chronic, indolent forms of NHL. This is reflected in the relatively small difference between both subtypes in our population. Nevertheless, in contrast to a previous study (Blaes et al., 2011), the group difference validated QoL measures in NHL. As an advantage of the restricted recruitment strategy, all the patients were undergoing congruent diagnostic and therapy procedures throughout the groups. Further, it resulted in a relatively small number of this rather frequent disease. However, we did not rely on surveys but could address the patients directly with trained raters and even study patients with advanced age or low functioning.

The factor and mediation analyses were explorative methods to better describe the data. To keep the analysis transparent, despite a high collinearity between the different measures associated with QoL, we did not conduct a factor rotation, which may have led to more pronounced loading in the smaller factors. Despite its explorative nature, the factor analysis was able to identify more specific research questions for future research: (1) cognitive impairments do not only reduce QoL but may interfere with the ability to address and cope with distress, (2) mapping of complex QoL measures on single scales (e.g. Distress Thermometer and SeiQoL) may lead to confounds with cognitive factors, and (3) measures of health-related psycho-physical well-being (e.g. FACT and HADS) are valid measures for distress in NHL.

6. Conclusions

In patients with NHLs, health-related QoL is lower in the patient group with aggressive than in those with indolent type. The group difference is mainly driven by a factor of interdependent emotional and physical well-being. Cognitive impairments as well as coping styles influence the reported distress and subjective QoL. Conceivably, patients with cognitive impairments or externalized locus of control are at risk for requesting and receiving less psychosocial and medical support.

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Competing interests

The authors declare no competing interest.

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