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Pre-treatment health-related quality of life parameters have prognostic impact in patients >65 years with newly diagnosed mantle cell lymphoma: The Nordic Lymphoma Group MCL4 (LENA-BERIT) experience

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Abstract

Mantle cell lymphoma (MCL) is a rare, often aggressive type of B-cell lymphoma with poor survival and no cure. Cancer and cancer treatment has a negative impact on health-related quality of life (HRQOL) both during active disease and in the long term, and improvement of HRQOL is a crucial objective of cancer therapy in older patients and no curative intent. Baseline HRQOL has in other lymphoma populations been shown to be predictive of outcome. Here, we explored HRQOL, and its association with survival, by the EORTC QLQ-C30 questionnaire, before, during and after chemotherapy in a patient cohort with MCL, treated within the NLG-MCL4 trial, designed to evaluate the addition of lenalidomide (LEN) to rituximab-bendamustine (R-B) as first-line treatment. Fifty-one patients were enrolled, median age was 71 years (range 62–84), 37 were men (73%). Pre-treatment HRQOL was similar to scores from the reference population with healthy individuals. During treatment, HRQOL deteriorated, but reverted to the same level as the reference population after treatment. There was a correlation between physical function ($p = 0.001$) and role function ($p = 0.006$) at baseline and WHO performance status, but not with other clinical or genetic prognostic factors. None of the baseline factors were predictive for treatment related to HRQOL in this cohort. Pre-treatment physical ($p = 0.011$) and role function ($p = 0.032$) were independent factors associated with overall survival, and physical function ($p = 0.002$) was also associated with progression free survival. These findings may possibly be used to design support during treatment and improve rehabilitation. Further investigations are needed for assessment of long-term HRQOL.

KEYWORDS

aged, disease-free survival, lymphoma, mantle cell, quality of life

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1 | INTRODUCTION

Mantle cell lymphoma (MCL) is an uncommon subtype of B-cell lymphoma, that constitutes approximately 3%–6% of all lymphoid malignancies. MCL is a heterogeneous disease spanning from indolent to aggressive course, often with short remission duration. Although survival of patients with MCL has improved since rituximab was introduced as part of standard treatment, it is yet not curable.^{1–4} Mantle cell lymphoma mostly affects men (70%), with a median age at diagnosis of 72 years.^{3,5} Most patients initially present with non-bulky lymphadenopathy and bone marrow involvement. Other extranodal involvement is also common, including tonsils, spleen, liver and the gastrointestinal tract.^{6,7} The MCL International Prognostic Index (MIPI), incorporating age, WHO performance status, leukocyte count (LPK), lactate dehydrogenase (LDH), and if available, Ki-67 proliferation index, may be used to divide the patients into three groups with different prognosis.^{8,9} Mantle cell lymphoma may also be divided according to more aggressive or more indolent disease based on genetic markers. The most important genetic prognostic marker in MCL is mutation of *TP53*, which is associated with markedly worse outcome also in patient treated with intensive treatment protocols. Another adverse genetic marker with less prognostic impact is deletion of *CDKN2A*.¹⁰

The mainstay of treatment for MCL is chemo-immunotherapy, and for younger patients, consolidation with autologous stem cell transplantation. Maintenance with rituximab has been shown to improve survival both for younger and older patients.^{11,12}

Quality of life is a broad concept of several dimensions, including different aspects of health. Health-related quality of life (HRQOL) is a narrower concept, focusing on the effects on physical, psychological, social and overall well-being in relation to a disease and given treatment.¹³ Questionnaires for HRQOL is a means for evaluating the patients' subjective experience of the treatment and total well-being, as a complement to survival and response rate.¹⁴ Cancer and cancer treatment have a negative impact on HRQOL both during active disease, and in the long term.^{15–17} In addition, baseline HRQOL has in other lymphoma populations been shown to be predictive of outcome.^{5,18–20} Hitherto, there are only few reports on HRQOL in MCL.

The current study was carried out in a population with patients over 65 years or not suitable for autologous stem-cell transplantation (ASCT) receiving a novel combination of lenalidomide in combination with rituximab and bendamustine in a Nordic phase Ib-II trial (LENA-BERIT). In this study, there was no impact of age or gender on overall OS or progression free survival (PFS). Similarly, performance status, stage of disease, level of LDH at diagnosis or MIPI did not affect outcome in this cohort,²¹ but the presence of a *TP53* mutation was associated with significantly worse outcome.¹⁰

The primary aim of this study was to explore HRQOL before, during and after chemotherapy in an older population of patients with previously untreated MCL in relation to a reference population and investigate its prognostic impact. Secondary aims were to identify predictors for HRQOL, information that may potentially be used for improvement in rehabilitation.

2 | METHODS

The cohort consisted of patients included in the multicenter open-label phase Ib-II NLG-MCL4 trial (LENA-BERIT), designed to evaluate the addition of lenalidomide to rituximab-bendamustine as first-line treatment in patients >65 years with MCL.²¹ The regimen consisted of lenalidomide plus rituximab-bendamustine for 6 months, followed by maintenance with lenalidomide for another 6 months. It was carried out in 14 centers in four Nordic countries (Sweden, Norway, Denmark, and Finland). The trial was performed in agreement with the Declaration of Helsinki and subsequent updates until 2008, according to the guidelines for Good Clinical Practice, issued by The International Conference on Harmonization (ICH). The protocol was approved by all national Ethical Review Boards. All patients signed a written informed consent. The study was registered at www.ClinicalTrials.gov as #NCT00963534.

2.1 | Health-related quality of life assessment

Health-related quality of life was assessed by the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, EORTC QLQ-C30 version 3, at baseline, and after 6, 12 and 24 months post study inclusion. In case of patient termination in the study, no more questionnaires were collected. EORTC QLQ-C30 constitutes of five functional scales, nine single symptom scales and global health status, in total 30 questions.²² The functional scales include physical, emotional, cognitive, social and role functioning. The symptom scales are fatigue, pain, nausea/vomiting, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. The questions are rated from 1 to 4 with scores corresponding from “not at all” to “very much”. Questions 29 and 30 are rated from 1 to 7 (“very poor” to “excellent”).^{23,24} For the functional scales and the global quality of life scale, a higher score represents a better level of functioning. For the symptom scales and single items, a higher score corresponds to a higher level of symptoms.²⁵ The validity and reliability of this questionnaire has been verified in several studies.^{26,27} Missing data were estimated, if more than half of answers in a scale were missing the scale was excluded. Raw scores were transformed to a linear scale ranging from 0 to 100 to be able to compare the scales.²³ Patient scores were compared to scores from an age- and sex-matched reference population of healthy individuals at baseline. A change of 10 or more scale scores was considered as clinically significant.²⁸

2.2 | Statistical methods

The differences between groups were tested using Mann-Whitney's *U*-test and Wilcoxon signed rank test. All hypothesis tests were conducted at the significance level of 0.05. OS was defined as time from trial registration in the LENA-BERIT study to death from any cause. PFS was defined as the interval between registration date and

date of documented progression, lack of response or first relapse. OS and PFS was analyzed by Kaplan–Meier estimates, and comparisons between groups were made by log rank test. Cox regression was used to study the relation between survival and baseline factors, including HRQOL, both for univariate analyses, and for multivariable models. Covariate analysis in multivariate models were mutation in *TP53* and deletion in *CDKN2A*. Multiple regression analysis was used for adjusting for factors that might affect the association. For illustration of the impact of baseline HRQOL in the Kaplan–Meier curves, the population was divided into two groups, with the median as cut-off values. For analysis of predictors for HRQOL, the association between factors at baseline and HRQOL at 6 months were tested, different type of test was chosen depending on type of variable. When the variable consisted of two groups, the Mann–Whitney's *U*-test was conducted, when it consisted of three or more groups Jonckheere–Terpstra trend test was used, and for continuous data, Spearman's rank-order correlation were chosen. For statistical analyses, SPSS version 26 and version 27 were used.

3 | RESULTS

Fifty-one previously untreated patients with MCL were enrolled between October 12, 2009, and May 22, 2013. One patient was excluded due to screen failure. Two patients did not fill in the EORTC QLQ-30 at baseline and were therefore excluded, which gives a cohort of 48 patients. Median age was 71 years (range 62–84), 37 were male (73%). Stratified according to MIPI; 5 (10%) were low-risk, 18 (38%) intermediate and 26 (52%) high-risk (Table 1). Median follow-up time for patients alive was 52 months. Twelve patients (24%) received the complete treatment (13 cycles), and 37 patients (73%) the induction phase (six cycles).

The proportion of patients reporting HRQOL was at baseline; 96% (48 of 50 patients), after 6 months (after induction phase); 83% (33 out of 40 patients alive), after 12 months (after maintenance phase); 89% (24 out of 27 patients alive), and after 24 months (1 year after treatment stopped); 75% (12 out of 16 patients alive). Twelve patients fulfilled all four questionnaires. The causes for treatment discontinuation were toxicity ($n = 28$ [74%], 15 during the induction phase), progressive disease ($n = 6$ [16%], five during the induction phase), second primary malignancies ($n = 3$ [8%]), and consent withdrawn ($n = 1$). Two patients received treatment outside the study among those who stopped treatment because of toxicity.

In total, there were 117 questionnaires available. Four scales from different patients at different timepoints were excluded due to missing values (missing values: 4 scales of 1755 scales, 0.2%). Another six questions had missing data, but approximation was possible to make.

Among the 12 patients who completed all four questionnaires, 10 were male (83%), with a median age of 73 years (range 62–80). Seven patients (58%) completed treatment (13 cycles), and five patients (42%) received less than 13 cycles.

TABLE 1 Patients' characteristics

Characteristic	
Age median (range)	71 (62–84)
Male/female	37/13 (73/27)
MIPI risk group, <i>n</i> (%)	
Low	5 (10)
Intermediate	19 (38)
High	26 (52)
Extranodal sites (<i>n</i>)	
0	9
1	24
2	10
3	3
4	3
Missing data	2
WHO performance status, <i>n</i> (%)	
0	25 (50)
1	22 (44)
2	3 (6)
Ann Arbor stage, <i>n</i> (%)	
II	2 (4)
III	4 (8)
IV	44 (88)
Completed treatment, <i>n</i> (%)	
Induction (1–6 cycles)	22 (44%)
Induction and maintenance (13 cycles)	16 (32%)
Completed EORTC QLQ-C30, <i>n</i> (%)	
Baseline	48 (96%)
After 6 months	33 (83%)
After 13 months	24 (89%)
After 25 months	12 (75%)

Abbreviation: MIPI, Mantle Cell Lymphoma International Prognostic Index.

3.1 | Longitudinal health-related quality of life

Before treatment, patients exhibited score levels comparable to the reference population or better (Table 2). During the first 6 months of treatment, several functional scores deteriorated. The change for physical function was statistically ($p < 0.05$), but not clinically significant (<10 scale scores), and the changes for role function, emotional function and cognitive function were clinically significant (>10 scale scores) (Figure 1). After 12 months, score levels had stabilized at baseline level or better. Social function and global quality of

TABLE 2 Scale scores of health-related quality of life, median values

	Baseline (IQR)	After 6 months (IQR)	<i>p</i> value baseline– 6 months	After 12 months (IQR)	<i>p</i> value 6– 12 months	After 24 months (IQR)	<i>p</i> value 12– 24 months	Reference population score
Functional scales of EORTC QLQ-C30								
Global QoL	75 (58–83)	75 (50–88)	0.47	83 (63–100)	0.004*	75 (52–83)	0.13	70
Physical function	87 (67–93)	80 (60–93)	0.007*	87 (80–100)	0.019*	87 (80–100)	1.0	74
Social function	83 (67–100)	83 (79–100)	0.52	100 (83–100)	0.031*	100 (86–100)	0.75	81
Role function	83 (67–100)	67 (50–100)	0.08	100 (75–100)	0.07	100 (67–100)	1.0	72
Cognitive function	100 (71–100)	83 (83–100)	0.57	100 (83–100)	0.71	84 (84–100)	1.0	79
Emotional function	83 (75–100)	92 (75–100)	0.47	92 (75–100)	1.0	100 (83–100)	0.08	86
Overall QoL	84 (74–92)	84 (71–92)	0.086	91 (85–96)	0.003*	94 (86–96)	0.32	-
Symptom scales of EORTC QLQ-C30								
Pain	17 (0–33)	0 (0–17)	0.35	0 (0–17)	1.0	0 (0–13)	0.75	26
Fatigue	33 (22–53)	33 (22–57)	0.54	33 (0–33)	0.002*	22 (11–33)	0.65	33
Nausea, vomiting	0 (0–13)	0 (0–17)	0.3	0 (0–0)	0.014*	0 (0–0)	1.0	5
Dyspnea	33 (0–58)	0 (0–33)	0.05*	0 (0–33)	0.4	17 (0–33)	1.0	25
Insomnia	0 (0–33)	0 (0–0)	0.15	0 (0–33)	0.6	0 (0–33)	0.5	26
Appetite loss	0 (0–0)	0 (0–33)	0.1	0 (0–0)	0.004*	0 (0–0)	1.0	11
Constipation	0 (0–33)	14 (0–33)	1.0	0 (0–0)	0.22	0 (0–25)	1.0	20
Diarrhea	0 (0–25)	0 (0–33)	0.88	0 (0–0)	0.002*	0 (0–0)	1.0	10
Financial difficulties	0 (0–0)	0 (0–0)	1.0	0 (0–0)	1.0	0 (0–0)	0.25	9

Note: Measured by questionnaire EORTC QLQ-C30 at baseline and after 6, 12 and 24 months post study inclusion, divided into functional scales and symptom scales. *p* value shown for the difference between consecutive questionnaires.

Abbreviation: QoL, quality of life; IQR, interquartile range.

*Significance level 95%.

life remained stable during the induction treatment, and both improved 12 months after start of treatment. The global quality of life score level increased above baseline after 12 months and reverted to baseline after 2 years.

The only functional scale that showed a lower score compared to baseline after 2 years was cognitive function, but the score at 2 years was not different from the cognitive function score of the reference population.

The symptom scores were comparable to the reference population at baseline. Six months after start of therapy, the score for constipation was impaired, whereas symptoms of pain and dyspnea had normalized. The score for pain was both clinically and statistically improved compared to baseline, but dyspnea only clinically. The other symptom scores were unchanged. After 12 months, the reported symptom scales had improved to a level superior compared both to baseline and to the reference population.

The same pattern is seen in the 12 patients who fulfilled all four questionnaires of HRQOL but here the decrease at 6 months is more distinct, Tables S1 and S2. The reduction in physical function (*p* value 0.037) and role function (*p* value 0.004) between baseline and after 6 months are both statistically (*p* value; physical function 0.037, role function 0.004) and clinically significant (>10 scale scores). The global quality of life, role function and emotional function shows a clear improvement after 6 months.

3.2 | Health-related quality of life and outcome

The prognostic impact of different HRQOL scale scores showed an association between improved OS and higher baseline levels of role function, social function, and pain, in univariate analysis (Table 3) (Figure 2). For PFS, a univariate analysis showed an association with

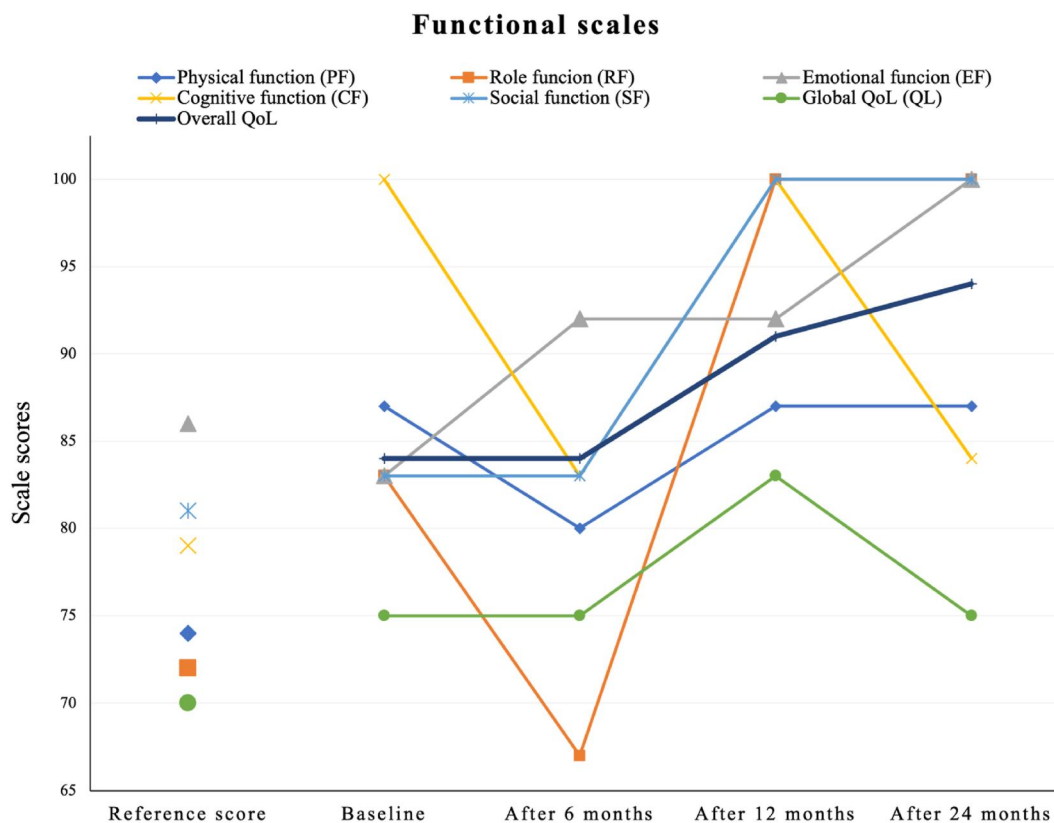


FIGURE 1 Functional scales over time, median values

improved PFS and higher baseline scores of role function and overall quality of life, and with lower scores for pain and appetite loss. In the subgroup if 12 patients answering four HRQOL no significance was found in univariate analysis.

In a multivariate model, adjusted for *TP53* and *CDKN2A*, both poor baseline physical function and role function were associated with impaired OS. In addition, poor physical function was associated with lower PFS. There was a correlation between physical function ($p = 0.001$) and role function ($p = 0.006$) at baseline and WHO performance status, but not with other clinical or genetic prognostic factors. The factors *TP53* mutation and *CDKN2A* deletion were included in the multivariate analysis since they were the only factors associated with PFS and OS in the univariate analysis. In this cohort neither age, gender nor performance status affected the outcome.

3.3 | Predictors of health-related quality of life impairment

Predictors for HRQOL were evaluated for physical function and role function. These two scales were chosen because they both were associated with OS in the multivariate model. Correlation between the HRQOL scales after 6 months and the variables gender, age at diagnosis, WHO performance status, LPK and LDH at baseline were tested. These variables were chosen because they are known to be

predictive of the prognosis. None of the baseline factors were predictive for treatment related to HRQOL.

4 | DISCUSSION

In this paper, we assessed HRQOL in a population of previously untreated older patients with MCL, receiving first line therapy, including lenalidomide in combination with rituximab-bendamustine. The proportion responding to the questionnaire was high, 75%–96% during the study, and there were few missing data or excluded scales. There were several notable findings. Pre-treatment HRQOL was comparable to an age and gender matched reference population, which may sound surprising, as the patients all were diagnosed with an incurable hematological malignancy. One possible explanation is response shift, that is a change in the meaning of one's self-evaluation due to a change in the internal standards of measurement. Moreover, patients enrolled in a clinical trial may constitute a population selected for superior performance status and possibly being more optimistic than a general patient population.

During treatment, HRQOL deteriorated, but reverted to the same level as the reference population 1 year after completing or stopping treatment, indicating either improved well-being after conclusion of chemotherapy or response shift. In contrast to previous studies, where survivors of non-Hodgkin lymphoma still are affected by the alterations in quality of life and social life 2 years after

	Univariate			Multivariate		
	p value	Hazard ratio	95% CI	p value	Hazard ratio	95% CI
Prognostic factors for OS in univariate and multivariate analysis						
TP53 mutation	0.001*	7.2	2.37–22.1			
CDKN2A deletion	0.043*	2.6	1.0–6.4			
Physical function	0.46	0.99	0.96–1.0	0.011*	0.96	0.93–0.99
Role function	0.012*	0.98	0.97–0.99	0.032*	0.98	0.97–1.0
Social function	0.039*	0.98	0.97–0.99	0.13	0.98	0.97–1.0
Pain	0.017*	1.0	1.0–1.0	0.17	1.0	0.99–1.0
Appetite loss	0.43	1.0	0.99–1.0	0.67	1.0	0.98–1.0
Overall QoL	0.073	0.99	0.94–1.0	0.39	0.99	0.95–1.0
Prognostic factors for PFS in univariate and multivariate analysis						
TP53 mutation	0.003*	4.6	1.7–12.8			
CDKN2A deletion	0.11	1.9	0.85–4.4			
Physical function	0.27	0.99	0.97–1.0	0.002*	0.96	0.94–0.96
Role function	0.029*	0.99	0.98–1.0	0.071	0.99	0.98–1.0
Social function	0.32	0.99	0.98–1.0	0.87	0.99	0.98–1.0
Pain	0.02*	1.0	1.0–1.0	0.093	1.0	1.0–1.0
Appetite loss	0.016*	1.0	1.0–1.0	0.34	1.0	0.99–1.0
Overall QoL	0.013*	0.97	0.94–0.99	0.092	0.98	0.95–1.0

Note: The multivariate model was adjusted for status of *TP53* mutation and *CDKN2A* deletion. All the variables of health-related quality of life are continuous.

Abbreviations: OS, overall survival; PFS, progression free survival; QoL, quality of life.

*Significance level 95%.

treatment, patients in our cohort recovered from the deterioration in HRQOL detected during therapy.^{29–32}

It is important to distinguish between statistical and clinically relevant associations. Several function scores (role function, emotional function, and cognitive function) showed both clinical and statistical significance, implying that the results are not only statistical correlations. Particularly the physical function, adjusted for mutations, might be used as indicators for outcome.

Pain is usually not a prominent symptom in lymphoma, although it may be more common than expected. Here, we show that pain improved both clinically and statistically during the first 6 months of treatment. The symptoms of dyspnea also diminished clinically the first 6 months. Constipation was the only symptom that worsened during treatment, possibly due to antiemetic medication or immobilization. Interestingly, cognitive function was the only scale showing lower levels compared to baseline in 2 years, indicating a possible long term cognitive effect of this regimen.

However, as the number of cases at later timepoints was low, the results during the later phase of the treatment should be interpreted with caution.

Pre-treatment physical and role function were both shown to be independent factors for OS, even when adjusted for *TP53* mutation and

CDKN2A deletion. In addition, physical function was an independent factor for PFS, even when adjusted for *TP53* mutation and *CDKN2A* deletion. This confirms previous observations in studies of patients with other types of lymphoma, showing similar associations between HRQOL and clinical outcome.^{19,20} There are two previous studies comparable with ours. One study demonstrated that improvement in well-being in patients with MCL was associated with treatment response,⁵ which indicate that baseline HRQOL may be used as a tool for measuring disease burden. The other study used the same treatment combination, lenalidomide-R-B, as in our study, in patients with aggressive B-cell lymphoma and found that pre-treatment impaired functional status was a prognostic factor for clinical outcome.¹⁸

WHO performance status and age were not significant prognostic factors in this cohort, but their prognostic impact may have been underestimated, since the cohort is quite small and constitutes of a specific age group with good performance status, as both performance status and age are established prognostic factors for MCL in larger cohorts.^{4,8,9}

We found no factors at baseline to be predictive of HRQOL after 6 months of treatment. This may reflect a high variability among the patients or a small sample. The results are in line with previous studies.²⁹

TABLE 3 Prognostic factors for overall survival and progression free survival

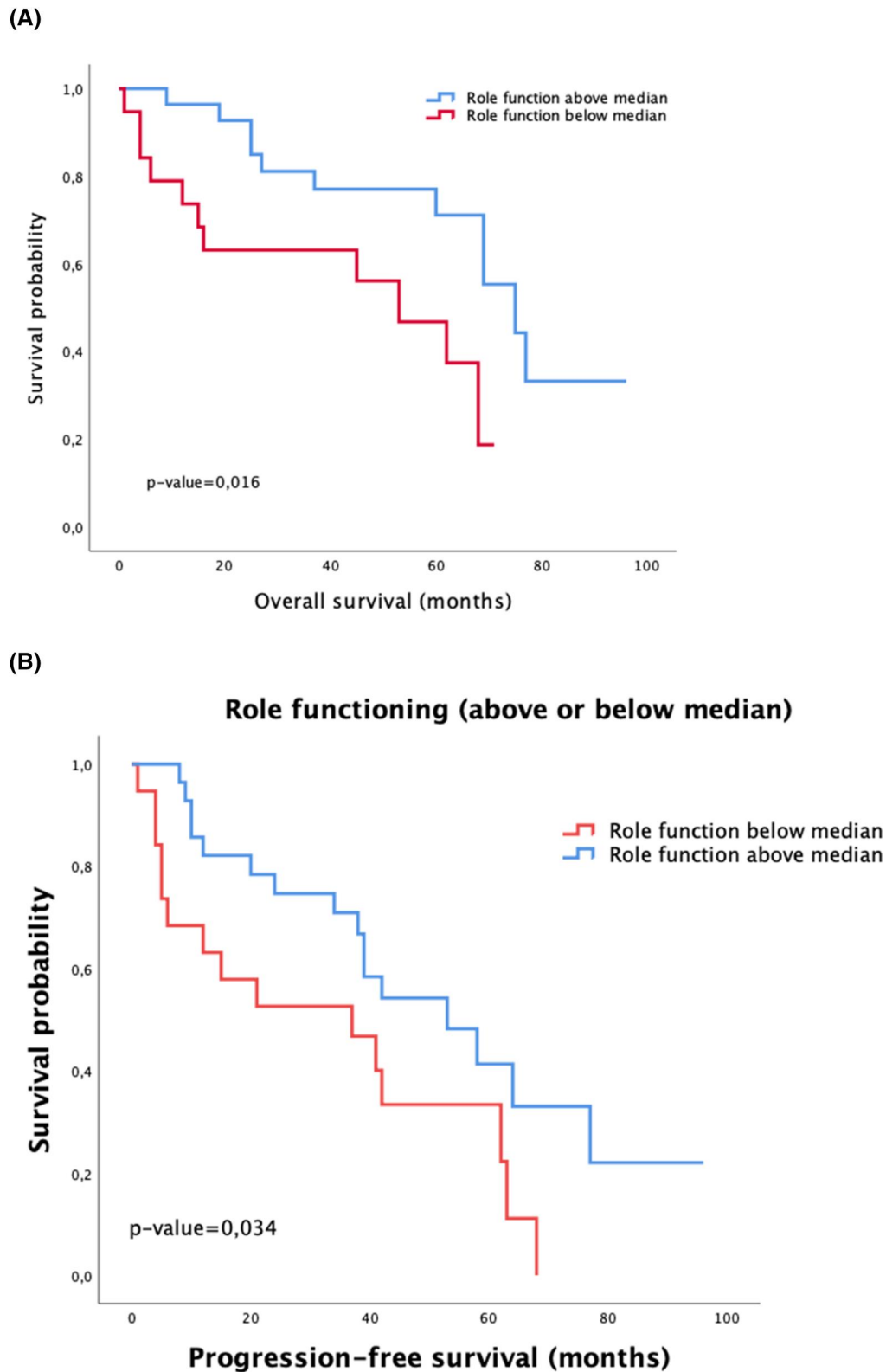


FIGURE 2 Overall survival. (A) Progression free survival, (B) for patients with role function above or below median

A strength of the current study is that HRQOL was investigated both before, during and after treatment and compared with a reference population. Among limitations, the study cohort was relatively small. Furthermore, the number of patients reporting HRQOL

data diminished over time, as patients discontinue treatment, causing a bias by selecting the individuals with more favorable outcome toward the end of treatment. Moreover, this trial used an experimental treatment regimen associated with increased toxicity compared to

current standard regimens and may not entirely reflect the HRQOL of MCL patients receiving standard treatment strategies. Further investigations are needed for evaluating long-term HRQOL and to explore if HRQOL can be improved with more efficient treatment or by better patient support. There is an ambitious ongoing project in France, aiming to follow patients with MCL indefinitely, collecting medical information and quality of life,³³ that may help to shed light on this issue.

Evaluation of HRQOL during treatment may provide a tool for enabling improved support and rehabilitation for lymphoma survivors. More than 65% of non-Hodgkin lymphoma survivors experience insufficient support from others,¹⁹ indicating that this is an area where there is room for improvement. Investigation of HRQOL has several limitations inherent in the design of the questionnaires. It is a subjective snapshot with recall bias, fixed questions, and no opportunity to make sure the patients understood the question. At a Consensus Conference by the European Society for Medical Oncology (ESMO) on treatment and care of elderly patients with lymphoma, quality of life was identified as one out of four important aims of the treatment.³⁴ Our study may contribute to the base of knowledge of quality of life in this patient population.

5 | CONCLUSION

In a population of patients with MCL, over 65 years or not suitable for ASCT, pre-treatment HRQOL was comprehensive to scores of an age matched reference population. Pre-treatment physical and role function were independent prognostic factors for outcome. These findings may be used to design support during treatment and improve rehabilitation. Further investigations are needed for assessment of long-term HRQOL.

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CONFLICT OF INTEREST

Mats Jerkeman received honoraria from Janssen-Cilag and Celgene and played a consulting and advisory role for Gilead Sciences. The remaining authors declare no competing financial interests.

AUTHOR CONTRIBUTIONS

Åsa Lindberg assembled data of quality of life and wrote manuscript draft; Arne Kolstad, Anna Laurell, Riikka Rätty and Mats Jerkeman conceived the design and collected and assembled data; and Alexandra Albertsson-Lindblad, Kirsten Grønabæk, Jan Sundberg (Department of Oncology, Skåne University Hospital, Lund, Sweden), Lone Bredo Pedersen (Department of Hematology, Rigshospitalet, Copenhagen, Denmark), Elisabeth Ralfkiær (Department of Pathology, Rigshospitalet, Copenhagen, Denmark), Marja-Liisa Karjalainen-Lindsberg (Department of Pathology, Helsinki University Central Hospital, Helsinki, Finland), Christer Sundström (Department of Pathology/Cytology, Lund University Hospital, Lund, Sweden), and Mats Ehinger (Department of Pathology/Cytology, Lund University Hospital, Lund, Sweden) collected and assembled data.

DATA AVAILABILITY STATEMENT

Data available on request from the authors.

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TRANSPARENT PEER REVIEW

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SUPPORTING INFORMATION

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