

# Assessment of Cognition and Quality of Life in Non-Hodgkin's Lymphoma Patients One Year Post-Treatment

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## Abstract

**Objectives:** An increasing number of patients with cancer are offered chemotherapy given either alone or in combination with radiotherapy, surgery, or both as neo-adjuvant, concomitant, or adjuvant treatment. Cognitive dysfunction is a prevalent side effect of cancer treatments that may persist for years following treatment and has negative impact on quality of life. Thus, the present study was planned to investigate the prevalence of cognitive impairment, assess the quality of life (QOL) and determine the socioeconomic status in NHL patients one year post chemotherapy treatment.

**Methods:** This was an observational study. All the prospective participants were screened on the basis of inclusion and exclusion criteria and the participants who met all the study inclusion criteria and had none of the exclusion criteria were enrolled in the study. Cognitive function was evaluated using Mini Mental State Examination (MMSE) or Hindi Mental State Examination (HMSE), socioeconomic status was determined by Kuppuswamy scale and quality of life (QoL) was assessed by EORTC QLQ.

**Results:** A total of 90 subjects (45 cases and 45 controls) were enrolled in the study. The control group scored more on MMSE/HMSE scale than the Non-Hodgkin's Lymphoma (NHL) patient group, suggesting difference in cognitive functioning between the groups ( $26.6 \pm 2.4$  vs.  $27.8 \pm 2.1$ ,  $p=0.019$ ), respectively. Socio-economic status did not have any impact on the prevalence of cognitive impairment in NHL patients; however, NHL was found to be more prevalent in upper-middle class. No significant difference was found between case and control for QoL.

**Conclusion:** Cognitive dysfunction is a prevalent side effect of cancer treatment that may persist for a year following treatment. Further studies are needed to clarify the effect on quality of life.

**Keywords:** Cognitive impairment; Non-hodgkin's lymphoma; Quality of life; Socioeconomic status

## Introduction

Cancer forms a leading cause of death worldwide. It is the second largest non-communicable disease and has a sizable contribution in the total number of deaths around the globe [1]. The world's population is expected to be 7.5 billion by 2020 and it's predicted that about 15 million new cancer cases will be diagnosed [2]. Non-Hodgkin's Lymphoma (NHL) has slowly grown from a rare to the fifth most common cancer in the world [3], however, the incidence rates of NHL are very low in India. As per the estimates, there are approximately 23,718 new NHL cases reported each year in India [4]. NHL incidence is rising with the current figure being 5.1 per 100,000 in urban registries [5].

Most of the patients with cancer are offered chemotherapy either alone or in combination with surgery, radiotherapy, or both as neoadjuvant, adjuvant, or concomitant treatment. Although the field of cancer therapeutics has advanced, chemotherapy holds its place as the mainstay therapeutic modality. Moreover, the recent progress in chemotherapy has resulted in improved management of various cancers [6]. Treatment alternatives for aggressive NHL include multi-agent chemotherapy, radiation, stem cell and or bone marrow

transplant. Enhanced treatments have emerged, resulting in prolonged survival and better control of disease and treatment associated complications [7].

However, these cytotoxic therapies despite being valuable in the treatment of malignancies, cytostatic agents, besides affecting cancer cells, also affect healthy cells in the body which are generally associated with some immediate or otherwise delayed side effects including nausea, vomiting, and fatigue [6-9], pain, insomnia, and appetite loss due to which the patients' health-related quality of life (HRQoL) can be significantly compromised [7].

Patients with cancer experience a lot of behavioral alterations that include anxiety, depression, fatigue, cognitive dysfunction, and sleep disturbances. These behavioral co-morbidities are possible throughout the process of diagnosis and treatment for cancer and may persist in the survivorship period as well. There is a rich literature describing probable consequences of behavioral co-morbidities in cancer patients including impaired QoL, reduced treatment adherence and increased disease-related morbidity and mortality. The adverse effects of chemotherapy treatment on QoL are well documented [10]. As the survival of cancer patients has increased, the impact of memory and executive function impairment, is gaining an immense concern on returning to everyday life. Risk factors include high dose exposure, use of multiple agents, and intra-arterial or intrathecal administration [11].

However, some studies have examined psychological impact of treatment among NHL survivors and its effect on their QoL, but in Indian population scarcity of data has been noticed. Additionally, a vast data related to cognitive impairment in different types of cancer is available. Many studies have been conducted to assess cognitive function in patients with breast cancer, testicular cancer, ovarian cancer, primary central nervous system lymphoma, however, there is scarce data related to cognitive functioning in Non-Hodgkin's lymphoma. Thus, the present study was planned to investigate the effect of chemotherapy on cognitive function and QoL in patients with NHL undergone. Additionally, the socioeconomic status will be assessed. With this evidence, we planned our study with one year post-treatment.

## Materials and Methods

This was an observational case-control study which was conducted in a tertiary care hospital, Rajiv Gandhi Cancer Institute and Research Centre, India. All the prospective participants were screened on the basis of inclusion and exclusion criteria and the participants who met all the study inclusion criteria and had none of the exclusion criteria were enrolled in the study, after giving informed consent. Cognitive function was evaluated using Mini Mental State Examination (MMSE) or Hindi Mental State Examination (HMSE), socioeconomic status was determined by Kuppuswamy scale and quality of life (QoL) was assessed by European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ).

## Study participants

### Cases:

Inclusion criteria:

Patients having age between 18-65 years.

Both males and female patients.

Patient having histologically and cytologically confirmed Non-Hodgkin's Lymphoma.

Patient capable of giving informed consent.

Patient willing to participate in the study.

Exclusion criteria:

Patients with history of major depression.

Patients with history of head injury.

Patients had evidence of uncontrolled clinical diseases, including diabetes, rheumatologic diseases, asthmatic diseases or other chronic inflammatory conditions.

Patients having cancer other than NHL.

Patients having neuropsychiatric disorders.

Patients with habit of any substance of abuse.

Patients who are incompetent for interview and unable to give informed consent.

### Controls:

Inclusion Criteria:

Subjects having age between 18-65 years.

Males and Females.

Subjects who are willing to give informed consent.

Exclusion criteria:

Subjects having evidence of uncontrolled clinical diseases, including cardiovascular diseases, diabetes, rheumatologic diseases, asthmatic diseases or other chronic inflammatory conditions.

Subjects having history of cancer.

## Clinical data

Social and demographic details including age, gender, height, weight, marital, employment and education status of the study participants were recorded in the case report form. Additionally, type of NHL, stage, co-morbid illness and clinical laboratory data were also recorded.

## EORTC QLQ C-30

Most extensively used instrument to measure the QoL in Cancer patients is the EORTC QoL C-30. The first EORTC QoL C-30 validation paper was published in 1993 [12]. This has been translated and validated in to 81 languages and is used in more than 3000 studies worldwide it is validated on Indian population [13].

## Mini-mental state examination

The Mini-Mental State Examination (MMSE) is the most widely administered psychometric screening assessment of cognitive functioning. It is a short and easy-to-administer test of a person's intellectual capacities. Any score  $\geq 24$  points (out of 30) indicates a normal cognition. Below this score, indicates severe (0-17) or mild (18-23) cognitive impairment [14].

## Hindi mini-mental state examination

The MMSE has bias with respect to education and language [15]. Thus, to counter this bias in India among rural and illiterate elderly, a modified version of MMSE, the HMSE, was developed. It is a tool developed by the IndoUS Cross-National Dementia Epidemiology Study, composed by 23 items which examine various cognitive capacities [16] (orientation to time and place, memory, concentration, attention, recognition of objects, language function, comprehension and expressive speech, motor functioning and praxis).

## Kuppuswamy scale

Socioeconomic status (SES) is a combined measure of a person's work experience economically and sociologically and of a family's or individual's economic and social position in relation to others, based on education, occupation, and income [17]. It is extensively used to assess the SES of an individual in the urban community and is based on three variables-occupation, education and income. Scorings are done for different levels of qualifications, occupations and family incomes per month. Accordingly, the socio-economic classes are divided into upper, middle and lower classes [18].

## Data analysis

Descriptive statistics has been used for meaningful interpretation of data. Mean and Standard Deviation was calculated for quantitative

data like gender, marital status and educational status while percentage was used for qualitative data. Chi-square tests have been applied for socio-demographic variables like gender, marital and educational status between NHL survivors and control group. Student's t-test was applied to found statistical significance between NHL survivors and control for QoL. P-value less than 0.05 was considered significant. One way Analysis Of Variance (ANOVA) has been used to find out statistical difference between EORTC QLQ C-30 and educational status. Correlation of EORTC QLQ C-30 with age was done with Spearman's rho correlation method. The correlation between age and MMSE/HMSE and Kuppusswamy has been assessed by scatter-plot and calculated by Pearson's/Spearman's correlation. The p-value less than 0.05 ( $p < 0.05$ ) will be considered significant. The reliability of the score variables (MMSE/HMSE, Kuppusswamy, Orientation, Registration, Attention and Concentration, Recall and Language) is measured by Cronbach's Alpha.

## Results

### Subjects

A total of 90 individuals participated in the study. The study comprised two groups: cases and controls. Forty five patients having histologically and cytologically confirmed Non-Hodgkin's Lymphoma were enrolled as cases and the control group included 45 individuals.

### Demographics

Of the 90 subjects enrolled in the study, 63 (70.0%) were men and 27 (30.0%) were women (Table 1). The mean  $\pm$  SD age of the subjects was  $50.8 \pm 11.1$  years.

	Control (%) 45 (100)	Case (%) 45 (100)	Total (%) 90 (100)	Chi-square	P value
Gender					
Male	32 (71.1)	31 (68.9)	63 (70.0)	0.05	0.818
Female	13 (28.9)	14 (31.1)	27 (30.0)		
Marital Status					
Married	43 (95.6)	42 (93.3)	85 (94.4)	0.212	0.645
Unmarried	2 (4.4)	3 (6.7)	5 (5.6)		
Educational Status					
Illiterate	5 (11.1)	2 (4.4)	7 (7.8)	5.732	0.125
Middle	12 (26.7)	5 (11.1)	17 (18.9)		
Intermediate	5 (11.1)	6 (13.3)	11 (12.2)		
Graduate & above	23 (51.1)	32 (71.1)	55 (61.1)		
Socio-economic status					
Lower Middle	(3) 6.7%	(4) 8.9%	(7) 7.8%	1.787	0.854
Lower	(0) 0.0%	(1) 2.2%	(1) 1.1%		
Upper	(8) 17.8%	(10) 22.2%	(18) 20.0%		
Upper Lower	(3) 6.7%	(2) 4.4%	(5) 5.6%		
Upper Middle	(31) 68.9%	(28) 62.2%	(59) 65.6%		

**Table 1:** Socio-demographic variables of case and control group.

### Prevalence of NHL based on socio-economic status

NHL was found to be more prevalent in the Upper Middle class society (Table 2).

Social class	Frequency	Prevalence	Percentage
Lower Middle	7	4	57.1
Lower	1	1	100.0
Upper	18	10	55.6
Upper Lower	5	2	40.0
Upper Middle	59	28	47.5
Upper Middle	59	28	47.5

**Table 2:** Prevalence of NHL based on socio-economic status.

### MMSE/HMSE score in patient group

The Mild Cognitive Impairment was demonstrated by 12% of the patient group which included 2 female patients and 3 male patients. This table summarizes the distribution of MMSE/HMSE scores based on gender. No statistical association was found between gender and MMSE/HMSE score. ( $p=1.000$ ). There was no statistically significant association found between the educational statuses of the patients and their score on MMSE/HMSE scale. ( $p=0.185$ ) (Table 3).

### MMSE/HMSE, Kuppuswamy and EORTC QLQ C-30 score of study group

While, a statistically significant difference was found between the patient group and control group ( $p=0.019^*$ ) in the MMSE/HMSE score, there was no statistically significant difference found between the patient group and control group in Kuppuswamy score ( $p=0.720$ ). There was no statistically significant difference in QoL among the two groups (Table 4).

	MMSE/HMSE Score		Total	Chi-Square	p-value
	Range				
	17-23	24-30			
Gender-wise				0.207	1.000
Female	(2) 40.0%	(12) 30.0%	(14) 31.1%		
Male	(3) 60.0%	(28) 70.0%	(31) 68.9%		
Total	(5) 100.0%	(40) 100.0%	(45) 100.0%		
Educational status					
Illiterate	(1) 20.0%	(1) 2.5%	(2) 4.4%	4.5	0.185
Middle School	(0) 0.0%	(5) 12.5%	(5) 11.1%		
Intermediate	(0) 0.0%	(6) 15.0%	(6) 13.3%		
Graduate & above	(4) 80.0%	(28) 70.0%	(32) 71.1%		
Total	(5) 100.0%	(40) 100.0%	(45) 100.0%		

**Table 3:** MMSE/HMSE Score in patient group.

	Cases Mean $\pm$ SD	Control Mean $\pm$ SD	t value	p- value
Kuppuswamy	21.6 $\pm$ 5.5	21.2 $\pm$ 5.7	0.360	0.720
MMSE/HMSE	26.6 $\pm$ 2.4	27.8 $\pm$ 2.1	2.399	0.019*
EORTC QLQ C-30	54.91 $\pm$ 9.01	52.04 $\pm$ 7.81	1.611	0.111

**Table 4:** Kuppuswamy, MMSE/HMSE and EORTC QLQ C-30 score of study group.

### MMSE/HMSE, Kuppuswamy and EORTC QLQ C-30 score of males and females in patient group

No statistically significant difference was found between the scores of males and females (Table 5).

	Male Mean $\pm$ SD	Female Mean $\pm$ SD	t value	P value
Kuppuswamy	23.0 $\pm$ 4.1	19.64 $\pm$ 4.5	1.08	0.312
MMSE/HMSE	26.7 $\pm$ 1.8	26.21 $\pm$ 2.1	1.13	0.286
EORTC QLQ C-30	52.34 $\pm$ 7.06	56.11 $\pm$ 10.90	1.65	0.108

**Table 5:** Kuppuswamy, MMSE/HMSE and EORTC QLQ C-30 score of males and females in patient group.

### Score in various domains of MMSE/HMSE of study group

Statistically significant difference found in the “Attention and Concentration” and “Recall” domains (Table 6).

Domains of MMSE/HMSE scale	NHL patients Mean $\pm$ SD	Control Mean $\pm$ SD	t value	p-value
Orientation	9.82 $\pm$ 0.3	9.82 $\pm$ 0.5	0.000	1.000
Registration	2.96 $\pm$ 0.2	3.00 $\pm$ 0.0	1.000	0.320
Attention and Concentration	3.38 $\pm$ 1.3	4.04 $\pm$ 1.3	2.356	0.021*
Recall	2.40 $\pm$ 0.9	2.76 $\pm$ 0.5	2.410	0.018*
Language	8.07 $\pm$ 0.9	8.20 $\pm$ 0.7	0.823	0.413

**Table 6:** Score in various domains of MMSE/HMSE of study group.

### The correlation between age and psychosocial variables in patient group

There was no statistically significant negative correlation found between age and the MMSE/HMSE score. Statistical analysis by

Spearman's rho correlation method reported significant correlation between age and quality of life. No significant difference was found between the different domains of educational status and QoL (Table 7).

Scale/Domain of scale	Age (yrs)	
	Correlation Coefficient	P-value
MMSE/HMSE	-0.221	0.145
Kuppuswamy	0.113	0.460
Orientation	0.162	0.288
Registration	-0.047	0.761
Attention and concentration	-0.180	0.238
Recall	-0.051	0.739
Language	-0.291	0.052
EORTC QLQ C-30	0.228	0.030 <sup>1</sup>

**Table 7:** The correlation between Age and Psychosocial variables in Patient group.

### Discussion

Previous studies have revealed that psycho-neurological symptoms, is very common in cancer survivors [19]. Despite of the fact that, many researchers have focused on QoL in patients stricken with cancer, to

our knowledge, this is one of the few studies comparing NHL patients with healthy controls to assess QoL.

This study has taken different factors such as age, education, gender and socioeconomic status under consideration to allow a rational



evaluation of cognitive impairment after treatment for NHL. Age is a well-established risk factor for cognitive decline in other diseases [20] and the researchers have reported that older adults may be more susceptible to cognitive adverse effects related to cancer treatments [21]. The study assessed the association between age and the psychosocial variables of patient group. Data suggests that no such statistically significant relationship was found in the patient group.

Information pertaining to gender differences in vulnerability to a disease is useful and can be used to develop preventive measures for a disease [22]. Males are more prone to develop cancer, and predominantly hematologic malignancies [23]. In the present study, the patient group had higher proportion of male patients (70%) than female patients (30%). Women's cognitive dysfunction may also be more severe than men's [24]. However there was no difference found between MMSE/HMSE score of male and female NHL patients.

In a study [25], the patients with early stage breast cancer having education less than high school were having higher risk of death. It also has been reported that there is a gap in life expectancy among women with low and high education regardless of race [26]. In another study, education was found to be positively associated with all-cause deaths [27]. The present study found no significant difference in the educational status of patient and control group. No significant association was found between the education status and the MMSE/HMSE score in the patient group.

Studies have shown that socioeconomic status (SES) has detrimental effect on our health. One of the most consistent findings in health outcomes including the death, are of socioeconomic differences. Income, Education and Occupation are components of socioeconomic status [27]. Significant effect of income and education on survival in the common population has been reported in a study [25]. SES may potentially affect progression of a disease. Therefore, socioeconomic disparities had been addressed in many clinical studies. A study conducted in survivors of childhood Leukemia showed that the children of lower SES did not seem to enjoy the survivorship very well [28].

The results of the present study suggest that Non-Hodgkin's Lymphoma was found to be more prevalent in Upper-Middle class and however no significant differences were found between the patient group and control group with respect to socioeconomic status. A study reported that up to thirty-five percent of cancer survivors show neuropsychological difficulties in across a wide range of domains [29]. Cognitive deficits are subtle and are probably the result of the common effects of cancer diagnosis and chemotherapy. Cancer survivors underwent chemotherapy displayed poor memory and attention than controls [30]. In a study of Breast cancer survivors, the survivors reported significantly more memory loss and displayed significantly poorer memory test performance than healthy controls. At an individual level, 17% of the survivor group had clinically significant impairment in the competence of new learning [31]. Various studies have shown that chemotherapy can stimulate changes in cognitive functions up to 5 years after treatment [32]. Since the present study had a small window period of one year, there was probability of finding Chemotherapy-related Cognitive Impairment (CRCI) in NHL patients. Findings of the present study are in line with the above mentioned clinical studies. In the study, 12% of the NHL patients were having Mild Cognitive Impairment (MCI). The results indicate poor memory and attention in patients with NHL than control group. The patients also displayed statistically significant impairment in the domain of Attention, Concentration and Recall. The neuropsychological tests data

indicates that in mean cognitive performance, there was statistically significant difference between patient and control group. Based on the individual impairment scores, a large difference was observed in the proportion of patients being classified as cognitively dysfunction, with a higher number in patient group (12%) and lower number in control group (7%).

Findings of the present study also provide an insight on HRQoL for NHL patients with one year post-treatment. Statistically, no significant difference was found between the cases and controls for HRQoL. This is in line with previous study, where no statistical difference for HRQoL was found between NHL survivors and general population [33]. QoL was found to be correlated with each other in several studies [34-36]. Few reported depressive mood as one of the variable that negatively affects QoL of cancer survivors [37]. However, no such correlation was found in our study. It was also found that patients often complained about pain in leg, irrespective of age, interfering in their daily activities hence effecting QoL. This is in accordance with study result reporting pain in cancer patients, influencing QoL [38]. Insomnia, loss of appetite and weakness were common symptoms reported by patients during their follow up. During the study, it was also observed that patients' perception towards cancer experience may influence their health status and functioning and QoL. Perceptions of greater health competence and personal control were persistently associated with higher HRQOL [35].

As the treatment advances, there is remarkable increase in survival rates as well as in the emotional needs of the patients. Early realization of psychological measures to be involved in the treatment process by healthcare professionals not only decreases the financial burden of cancer treatment but also helps in improving QoL [39].

This study also has some limitations which needs to be mentioned. The studied sample size was small in number. In this study patients were not assessed in a longitudinal design. Personality traits of the patients also have impact on the QoL which we did not assess. NHL survivors from Rajiv Gandhi Cancer Institute and Research Centre may not be representative of all Indian survivors and our reports may not generalize to the experiences of longer term survivors, thereby limiting the extrapolation of our results. Despite this, our study adds to the very limited literature on assessment of cognitive functions in NHL survivors providing a more comprehensive assessment of cognitive functions outcomes in the population than has been previously reported.

## Conclusion

This study demonstrated significant difference in cognitive function in NHL patients and controls. There is a need of including neuropsychological measures in the treatment to assess cognitive changes in patients and proper counselling sessions are required for patients to cope up with psychoneurological symptoms, thereby, enhancing their quality of life. It suggests the need of screening QoL in cancer patients along with the treatment. Further research is needed to investigate the lack of significant differences between other factors in HRQoL. Oncology healthcare providers need to be more proficient in psychosocial assessment and able to find signs, monitor risk factors and reduce cognitive impairment in cancer patients. Involvement of healthcare providers will improve quality of life and psychological distress in cancer patients.

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