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## Major depressive disorder and associated factors in elderly patients with non-Hodgkin's lymphoma

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### ABSTRACT

**Background:** Data regarding elderly patients with cancer, more particularly with non-Hodgkin's lymphomas (NHL), are scarce, as is our knowledge concerning to comorbid depression in this population. The purpose of this work was to explore the frequency of major depressive disorder (MDD) and related factors in a group of elderly patients with these forms of cancer.

**Method:** 42 elderly NHL patients aged 70 years and older were interviewed using the Mini International Neuropsychiatric Interview screening tool. Psychological variables such as coping strategies, cognitive status and quality of relationships, as well as clinical and socio-demographic data were collected.

**Results:** Fourteen patients (33.3%) met criteria for current MDD of which five had melancholy features (35.7%). Elderly patients with comorbid NHL-MDD had a significantly poorer self-perceived global health and performance status than those without MDD, as well as more fatigue and history of depression. No other clinical, psychological or socio-demographic variable appeared associated with MDD in this sample.

**Conclusion:** Further studies are needed in order to confirm these early results concerning a potential high frequency of MDD among elderly NHL patients. Depressive mood should be early recognized in order to provide appropriate treatments and avoid a detrimental effect of depression on cancer prognosis.

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Depression; cancer; non-Hodgkin's lymphoma; elderly

## Introduction

Older adults are particularly vulnerable to depression for several reasons, among which are social and emotional losses (e.g. retirement, widowhood), increase of physical dependence, decrease of cognitive performance (Justel & Ruetti, 2014) and the onset of chronic diseases (Frémont, 2004). In this regard, a frequent disease in later life is cancer, with increasing age

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constituting the most significant risk factor for its development (Lichman, Balducci, & Aapro, 2007). The prevalence of depressive disorders in cancer patients ranges from 20 to 50% (Pasquini & Biondi, 2007) while rates of major depressive disorder (MDD) are estimated as high as 38% (Weinberger, Bruce, Roth, Breitbart, & Nelson, 2011). According to Findley, Shen, and Sambamoorthi (2012), the elderly have not been specifically studied in works exploring depression in patients with cancer, which explains the scarcity of data in this specific population. A recent study (Cheng, Chan, Sham, & Li, 2014) reported significant depressive symptoms assessed with the Geriatric Depression Scale-Short Form (GDS-SF) (Sheikh & Yesavage, 1986) in 43.9% of 41 elderly patients with advance cancer (age  $\geq$  65). These symptoms were the most important independent factor for suicidality in this population. Hamilton et al. (2013) reported that based on scores on the GDS-SF, 11.7% of 77 older African American cancer patients (mean age = 58) were possibly depressed. The study of Agarwal, Hamilton, Moore, and Crandell (2010) in Afro-American older cancer survivors (mean age = 63.5), observed using the same instrument of the previous study, that 27.2% of participants ( $n = 283$ ) had scores indicative of depression. Findley et al. (2012) based on the International Classification of Disease (ICD-9) diagnostic criteria found that 5% ( $n = 865$ ) of their sample composed of elderly subjects with cancer (age  $\geq$  65) were diagnosed with depression including MDD, although its prevalence was not specified. Finally, Zhang and Cooper (2010) observed a rate of MDD of 0.2–0.4% in elderly colorectal cancer patients (age  $\geq$  65) according to the ICD-9 criteria.

Considering that depressive mood may have a negative impact on quality of life and that it has been associated with more rapidly progressing cancer symptoms, more metastasis and pain compared to non-depressed cancer patients (Hopko et al., 2008a) and higher rates of non-compliance with treatment plan (Ashbury et al., 2003), the early recognition and treatment of comorbid depression in cancer patients is a priority issue. Nevertheless, cancer patients over age 60 are under-treated of depression (Ashbury et al., 2003).

Furthermore, the few studies on depression in elderly cancer patients not always specify the type of cancer or cancer site, which is important to take into account as one of the most important factors associated with the prevalence of depression (Pasquini & Biondi, 2007). In this regard no study exists exploring the prevalence of depression, and more particularly MDD in elderly patients with non-Hodgkin's lymphoma (NHL), which are a group of malignancies that arise from lymphoid tissues (Caimi, Barr, Berger, & Lazarus, 2010) representing the fifth cause of cancer in France (Dupuis & Haioun, 2008).

The main objective of this study was to explore the frequency of MDD in a group of elderly patients with NHL. The second objective was to explore the clinical, psychological and socio-demographic factors associated with MDD in this population.

## Method

### Participants

Participants were men and women aged 70 years and older with a diffuse large B-cell NHL (the most common type of aggressive NHL), CD20 positive according to the classification of the World Health Organization (Harris et al., 1999), including all morphological and clinical variants and excluding Burkitt-like lymphoma. Exclusion criteria were: previously

treated patients, presence of cerebral and meningeal involvement, previous or concurrent second malignant solid tumor. The participants of this study were included between September 2009 and June 2012 from 13 centers in France.

### *Instruments and procedure*

The clinical and geriatric assessment included the Ann Arbor classification which is a system widely used to staging NHL according to the distribution of lymphatic involvement, the Cumulative Illness Rating Scale for Geriatrics (CIRS-G) to evaluate comorbidities and their severity (Extermann, 2000), the Mini Nutritional Assessment (MNA) to screen for malnutrition (Guigoz, Vellas, & Garry, 1994), the scale of the Eastern Cooperative Oncology Group (ECOG) to evaluate the performance status of patients (Oken et al., 1982), and the Multidimensional Fatigue Inventory (MFI) to assess general fatigue (Gentile, Delarozière, Favre, Sambuc, & San Marco, 2003). The psychological evaluation included sections of the French version of the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1989), which was used to ascertain the presence of MDD with or without melancholic features and to assess MDD in the past according to criteria of the Diagnostic and Statistical Manual (DSM)-III-R/IV Axis I disorders. The MINI is modeled on a clinical interview. All questions are dichotomous with a “yes” or “no” answer. Furthermore, the Mini Mental State (MMS) (Kalafat, Hugonot-Diener, & Poitrenaud, 2003) was used to assess the cognitive state of the patients. The French validated version of The Ways of Coping Checklist-R (WCC-R) (Cousson-Gelie et al., 2010) was applied to assess three coping strategies (problem-focused coping, emotion-focused coping and seeking social support). The Quality of Relationship Inventory (QRI) (Pierce, Sarason, & Sarason, 1991) was used to evaluate relationship-specific perceptions of social support (i.e. perceived availability of social support), conflict (i.e. negative dyadic interactions and ambivalence) and depth (i.e. positive interactions and feelings of closeness and security within the relationship), as the QLQ-C30 quality-of-life questionnaire which provides a self-rated measure of the global health status and the global quality of life (Aaronson et al., 1993). Psychologists at patients’ home or at hospital conducted the psychological assessment. Finally, socio-demographic data such as sex, age, marital status, number of children and schooling were also collected.

### *Ethics*

The study was conducted according to the ethical principles of the Helsinki Declaration of 1964, revised in 2004, and in agreement with local ethics requirements. An informed consent was obtained from all participants before entering the study.

### *Analysis*

Statistical analyses of the data included a descriptive analysis using mean, standard deviation, median and interquartile interval for continuous variables and frequencies and proportions for categorical variables. The comparisons of categorical variables between depressed and non-depressed patients were made using chi-square or Fisher’s exact test if chi-square was not a valid test. For continuous variables, the comparisons were

performed using the non-parametric Mann-Whitney U test. All statistical tests were two-sided and a  $p$  value of less than .05 was considered statistically significant.

## Results

The final sample was composed of 42 patients: 20 men and 22 females aged between 73 and 89 years (mean age = 81.6, SD = 4.2). More than half of patients (57.5%) were at stage IV of the disease (extranodal organ involvement) according to the Ann Arbor classification. The description of the whole sample is presented in [Table 1](#).

Fourteen patients (33.3%) met criteria for current MDD. Five of them (35.7%) present melancholy features.

The comparison between elderly NHL patients with and without MDD ([Table 1](#)) shows that these groups did not differ in terms of age and years of education. Most of patients with current MDD are females although the difference does not reach statistical significance ( $p = .08$ ). The performance status was significantly different between groups; among patients with MDD the percentage of participants with a strong reduction of activities and bed rest was superior to the percentage of participants with a mild reduction activities and ambulatory treatment (85.7% vs. 14.3%,  $p < .05$ ). The score of fatigue was significantly higher among patients with MDD (median of 15.5 vs. 13 for non-depressed patients,  $p < .05$ ), while the self-perceived global health status score was significantly lower among patients with MDD (median of 3 vs. 4,  $p < .05$ ). No differences were found between groups concerning psychological variables such as the coping strategies, cognitive status and quality of relationships. In contrast, the experience of a MDD in the past was significantly more frequent among participants with current MDD than in those without it: almost 70% of patients with current MDD were already depressed in the past.

## Discussion

Using a structured diagnostic interview, we found a prevalence of 33.3% of MDD in our sample of elderly NHL patients. Although no other reports exist about MDD in this specific population to make comparisons, this figure seems consistent with works reporting a high prevalence of MDD in cancer patients, which is estimated as high as 38% (Weinberger et al., 2011). In contrast, it exceeds rates of MDD observed in older primary care patients (6.5–9.0%) (Schulberg et al., 1998), and in the general older population in France (3%) (Ritchie et al., 2004).

In this study the assessment of MDD was made prior to cancer treatment, that is, near to the diagnostic announce, which is particularly important for clinical and prevention purposes. According to Agarwal et al. (2010), “when cancer patients experience depressive symptoms at the time of diagnosis, there is an increased likelihood of poor health outcome” (p. 2). In this regard, we observe that depressed patients of our sample declared a significantly poorer global health status than non-depressed patients as well as higher levels of fatigue, and this despite no differences between depressed and non-depressed patients concerning the extent of comorbid illness other than depression and the stage of cancer. At this point, our results are consistent with those of Bardwell et al. (2006), who observed that objective cancer-related variables such as the cancer stage were not associated with depressive symptoms in patients with breast cancer. Furthermore,

**Table 1.** Comparison of study variables between groups.

		All patients (n = 42)	Not depressed (n = 28)	Current MDD (n = 14)	p- value*
Sociodemographic variables					
Age		81.6 ± 4.2	80.5 [78.2–84.7]	84.0 [79.7–86.2]	.18
Sex	Male	20 (47.6)	16 (57.1)	4 (28.6)	
	Female	22 (52.4)	12 (42.9)	10 (71.4)	.08
Marital status	Married	22 (55)	16 (57.1)	6 (50.0)	
	Divorced / Single / Widowed	18 (45)	12 (42.9)	6 (50.0)	.67
Number of children		3.3 ± 2.7	2.0 [1.0–5.0]	3.0 [1.25 – 4.0]	.42
Schooling	< 8 years	13 (32.5)	10 (35.7)	3 (25.0)	
	≥ 8 years	27 (67.5)	18 (64.3)	9 (75.0)	.71
Geographical area	Northern France	20 (47.6)	13 (46.4)	7 (50.0)	
	Southern France	22 (52.4)	15 (53.6)	7 (50.0)	.82
Clinical variables					
Stage of the disease (Anne Arbor):	Stage II–III	17 (42.5)	11 (42.3)	6 (42.9)	0.97
	Stage IV	23 (57.5)	15 (57.7)	8 (57.1)	
Cumulative Illness Rating Scale (CIRS-G)		8.9 ± 4.4	8.0 [6.0–10.0]	7.0 [4.7–12.2]	.65
Number of drugs		7.2 ± 3.2	7.0 [5.0–9.0]	7.5 [4.7 – 10.2]	.59
Performance status (ECOG)					
	Mild activity reduction, ambulatory	15 (35.7)	13 (46.4)	2 (14.3)	
	Strong activity reduction, bed rest	27 (64.3)	15 (53.6)	12 (85.7)	<.05
Fatigue (MFI)		13 ± 3.5	13.0 [10.2 – 15]	15.5 [13 -19.2]	<.05
Malnutrition (MNA)	Yes	12 (31.6)	5 (20)	7 (53.8)	
	No	26 (68.4)	20 (80)	6 (46.2)	0.06
Psychological assessment					
Cognitive status (MMS)		23.7 ± 5.2	23.0 [20.7 – 29.0]	24.0 [23.0–28.0]	0.68
Depression in the past (MINI)	Yes	9 (22.0)	0 (0)	9 (69.2)	
	No	32 (78.0)	28 (100)	4 (30.8)	<.01
The Ways of Coping Checklist (WCC-R)					
	Problem-focused coping	19.5 ± 5.8	21.0 [16.5 – 24.5]	18.5 [12.0–24.0]	.45
	Emotion-focused coping	14.3 ± 4.5	13.0 [9.2–17.0]	15.0 [12.0–19.0]	.33
	Seeking social support	16.6 ± 5.1	15.0 [12.0–21.0]	17.0 [14.0–23.5]	0.21
Quality of Relationships Inventory (QRI):					
	Perception of social support	24.7 ± 4.0	25.5 [23.2–27.0]	27.0 [26.0–28.0]	0.17
	Conflict	17.9 ± 4.9	16.0 [14.5–18.7]	18.0 [14.0–21.0]	.55
	Depth	20.0 ± 2.6	20.0 [19.0–21.5]	21.0 [18.0–23.0]	.93
	Global health status (QLQ-C30)	3.8 ± 1.3	4.0 [3.0–5.0]	3.0 [3.0–4.2]	<.05
	Global quality of life (QLQ-C30)	4.0 ± 1.6	4.0 [3.2–5.7]	3.0 [2.0–5.0]	0.06

MDD = Major depressive disorder. Data are mean ± SD, median [Interquartile 25–75], or number (percentage). \* = Mann-Whitney test for continuous variables and Chi-square test for categorical variables.

among those with MDD in our study, there were significantly more patients with a strong reduction of activities and bed rest than with a mild reduction activities and ambulatory treatment. Thus, our results add to the weight of evidence demonstrating the dire consequences of depression combined to another chronic disease. As Weinberger et al. (2011) noted, depression worsens the distress experienced from symptoms. Moreover, elderly NHL patients of this study already face multiples comorbidities and polypharmacy (seven drugs on average in this study) and must add difficult treatments such as chemotherapy. Compliance in this context is a major issue, and depression can be detrimental to adherence with plan treatment as has been shown in previous studies (Ashbury et al.,

2003). All these aspects highlight the need of early recognition and treatment of mood disorder in these patients. Although this study focuses on MDD, other depressive disorders and even subsyndromal levels of depressive symptoms merit attention and should not be underestimated.

The overlap between some cancer symptoms or side effects induced by cancer treatments, and those of depression (fatigue, weight loss, sleep problems, etc.), and comorbidities makes particularly difficult the recognition of this mood disorder. In this regard, Cohen-Cole, Brown, and McDaniel (1993) distinguish two MDD diagnostics systems: the exclusive system in which anorexia and fatigue are removed from the DSM-IV criteria, and the inclusive system which includes all symptoms as was done in the present study. The exclusive system may increase the specificity of the diagnosis, while the inclusive system appears more appropriate for clinical purposes. Previous research has also shown that specific symptoms within the depression pattern, such as negative thoughts and anxiety, could help better identify clinical depression in older people with diabetes (Sultan, Luminet, & Hartemann, 2010). As Raison and Miller (2003) pointed out, cancer patients experiencing symptoms consistent with MDD can benefit of antidepressant therapy or of a combined modality approach including both pharmacologic and psychosocial interventions (Rodin et al., 2007), irrespective of if symptoms arise from depression or other sickness syndrome (Raison & Miller, 2003). Moreover, it has been showed that physical activity in cancer patients can have a positive impact on depression (Galiano-Castillo et al., 2014; Midtgaard et al., 2011). It could be interesting to test an exercise intervention adapted to elderly patients. Recently Walker et al. (2014) state that although more expensive than usual practice, the identification and treatment of MDD in cancer patients may generate more quality-adjusted life years than other medical interventions.

Another barrier to the diagnosis and treatment of depression in cancer patients is the still deeply rooted assumption among practitioners that it is natural for these patients to be depressed (Hopko et al., 2008b). Alike, it is mistakenly believed that depressed mood is part of aging. Thus, it is not surprising that depression in elderly cancer patients is under-diagnosed, under-treated (Hopko et al., 2008b; Rodin et al., 2007) and also under-researched. In this regard, history of depression as observed in most of patients with current MDD of our sample is a clue to identify those vulnerable to mood disorders. It is well known that a clinical aspect of depression is its recurrent nature. After a first depressive episode, more than half of patients have a second episode and the relapse rate increases subsequently after each decompensation (Olié & Courtet, 2010).

Psychological variables such as the coping strategies and perception of social support did not appear associated with MDD as observed in other reports (Ferreira et al., 2013; Hamilton et al., 2013; Pasquini & Biondi, 2007). A larger sample size could reveal differences in this domain, as well as the sex differences classically seen in depression prevalence (more prevalent in females) and in quality of life that in this study showed a trend to significance due to a lack of statistical power.

The results of the present work should be interpreted with caution as they are based on a small number of patients. Longitudinal studies in larger samples are needed in order to confirm these results and causality. Despite limits, this work addresses a gap in the literature as to the frequency of comorbid depression in elderly NHL patients. Furthermore, as Pasquini and Biondi (2007) pointed out, often prevalence of depression in cancer patients

is reported only on the basis of self-administered questionnaires, which provide less reliable measures than interviews or clinical explorations. In this sense, the use of a psychiatric structured diagnostic interview instrument (MINI) to assess MDD should be considered strength of this study.

Clinical implications: MDD is frequent among elderly patients with NHL, and it is associated with worst health status. Early recognition and treatment of depressive symptoms among these patients is necessary in order to prevent a negative impact on the course of disease. Thus, depressive symptoms should be routinely screened.

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