Psychological well–being in advanced NSCLC patients in Serbia: impact of sociodemographic and clinical factors

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Patients with advanced non-small cell lung cancer (NSCLC) usually undergo toxic treatment (chemotherapy and/or radiotherapy). They can experience devastating effects of illness and therapies on their psychological and emotional well-being. On the other hand, untreated psychological distress is associated with reduced quality of life and inadequate palliation of physical symptoms.

In order to estimate frequency of anxiety and depressive symptoms and influence of demographic, socioeconomic and clinical factors on psychological well-being, we performed this cross-sectional study in group of 100 patients with advanced stage of disease. Symptoms of anxiety and depression were assessed using the Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating scale (HDRS). Health-related quality of life data are obtained by EORTC QLC C30 and SF 36.

Patients with poor performance status (PS) experienced significantly more anxiety and depressive symptoms (p=0.001) and worse emotional (p=0.001) and mental functioning (p=0.001). Treated patients had significantly better mental (p=0.011) and emotional (p=0.001) functioning in compared to newly diagnosed ones. Somewhat unusual, unemployed participants reported significantly less anxiety (p=0.029) and depressive (p=0.002) symptoms, better mental (p=0.030) and emotional functioning (p=0.007). Additionally, nausea and vomiting adversely affected mental health and emotional functioning and correlated significantly positively with HARS and HDRS scores.

Our findings suggest significant impact of some disease-related factors (PS, active treatment) and treatment-related factors (chemotherapy - induced nausea and vomiting) on psychological well-being of patients with advanced NSCLC. This should be taking an account when appropriate interventions are planned.

Key words: lung cancer, anxiety, depression, quality of life, chemotherapy, chemotherapy-induced nausea and vomiting

Psychological distress is common in cancer patients, however, it is often unrecognized and untreated [1]. As many of half of all cancer patients experience depressive symptoms at a level that would qualify for clinical diagnosis [2]. There is good evidence that depression is a major problem in advanced stages of cancer patients [3, 4]. Studies of psychological distress in patients with advanced disease have reported a prevalence of affective disorders varying from 23% [5] to 47% [6], although these investigations usually carried out in heterogeneous patients' samples. Therefore, the effect of symptom patterns has not yet been fully elucidated [7]. At the time of diagnosis, advanced non-small cell lung cancer (NSCLC) (Stage IIIB, IV) is responsible for two-thirds of NSCLC cases [8]. Hence, advanced NSCLC is associated with poor prognosis; median survival in untreated patients with stage IV is approximately 4 months [9]. The psychological distress is pronounced es-

pecially among patients with lung cancer (prevalence rate 43.4%) in comparison with patients with other cancer sites [10]. Additionally, in lung cancer patients, especially in those with advanced stage of disease, higher rates of depression have been reported than in the general population [7, 11, 12], and it has been linked to decreased survival [13]. Despite the large number of patients with lung cancer who receive palliative treatment, there is a little published data concerning the prevalence of psychological distress in this group [7]. Yet, we know that emotional distress can worsen the impact of physical illness, threaten physical health, and interferes with providing medical treatment [14, 15]. On the other hand, it is very difficult to identify depression amongst patients with advanced illness because many of the symptoms of depression are difficult to evoke in patients who are approaching the end of life [16]. Untreated depression in the terminally ill is as-

sociated with reduced quality of life [17], increased difficulty in palliation of physical symptoms, elevated health care costs and increased mortality [18, 19].

In Serbia, there is a lack of available data of influence of anxiety and depression on patients with advanced lung cancer. Having in mind that economic disadvantages have significant influence on psychological well-being among patients with other chronic illnesses [20], we performed investigation in the group of Serbian patients with advanced NSCLC. Additionally, we used quality of life (QOL) data (obtained by EORTC QLQ C30 and SF 36), which contain important information about psychological distress and provide opportunity to explore these specific domains.

The aim of our study was to estimate frequency of anxiety and depression symptoms in patients with advanced lung cancer. Furthermore, we analyzed associations between depression and anxiety symptoms and demographic, socioeconomic and clinical factors.

Patients and methods

Patients. The cross-sectional study was conducted among 100 consecutive patients with advanced NSCLC (stage IIIB and IV) from outpatients and inpatients clinic settings at the Institute for Lung Diseases and Tuberculosis, Clinical Center of Serbia, Belgrade. All patients met the following criteria: histologicaly confirmed diagnosis of NSCLC, stage IIIB or IV (according to the American Thoracic Society TNM classification), and Karnofsky index ≥ 70%. The exclusion criteria were as follows: major concomitant diseases, previously diagnosed psychiatric diseases, existing of other malignant disease and unwillingness to participate. Toxicity was classified according to the World Health Organization criteria.

Instruments. Symptoms of anxiety and depression were assessed using the Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS). The both scales are interviewer-administered and rated measure. The Hamilton Anxiety Rating Scale is a 14-item test used to assess the severity of anxiety symptoms. It provides measures of overall anxiety, psychic anxiety (mental agitation and psychological distress), and somatic anxiety (physical complaints related to anxiety). The HARS is administered by trained interviewer who asked a semi-structured series of questions related to symptoms of anxiety. The interviewer then rated the individuals on a five-point scale for each of the 14 items. Seven of the items specifically address psychic anxiety and the remaining seven ones address somatic anxiety. For the 14 items, the values on the scale range from zero to four: zero means that there is no anxiety, one indicates mild anxiety, two indicates moderate anxiety, three indicates severe anxiety, and four indicates very severe or grossly disabling anxiety. The total anxiety score ranges from 0 to 56. Scores between 0 to 9 indicated absence of anxiety, scores between 10 and 17 indicated mild anxiety, scores between 18 to 24 indicated mild to moderate anxiety, scores between 25 to 31 indicates moderate to marked anxiety and scores over 31 indicated severe anxiety [21, 22].

The Hamilton Depression Rating Scale (HDRS) is a test measuring the severity of depressive symptoms. Besides the interview with the depressed patient, other information can be utilized in formulating ratings, such as information gathered from family, friends, and patient records. In the 21-item version, 11 items were scored on a five-point scale, ranging from 0 to 4. A score of 0 represents an absence of the depressive symptoms being measured, a score of 1 indicates doubt concerning the presence of the symptom, a score of 2 indicates mild symptoms, a score of 3 indicates moderate symptoms, and a score of 4 represents the presence of severe symptoms. The remaining 10 items are scored on a three-point scale, from 0 to 2, with 0 representing absence of symptom, 1 indicating doubt that the symptom is present, and 2 representing clear presence of symptoms. For the 21-item version, scores can range from 0 to 64. One formulation suggests that scores between 0 and 7 indicate a normal person with regard to depression, scores between 8 and 13 indicate mild depression, scores between 14 and 18 indicate moderate depression, scores between 19 and 22 indicated marked depression and scores over 23 indicate severe depression [21, 22].

Health-related quality of life (HRQoL) was assessed using Medical Outcomes 36-item Short Form Health Survey (SF-36) (Serbian version) which comprises eight subscales: Physical Functioning (PF), Role Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE) and Mental Health (MH). Based on these eight scales, two summary scales have been constructed: the Physical Component Summary (PCS) and the Mental Component Summary (MCS) [23]. Higher scores of SF-36 scales mean better quality of life. The EORTC QLQ C-30 is a 30-item questionnaire and includes five functional scales: Physical Functioning (PF), Role Functioning (RF), Emotional Functioning (EF), Cognitive Functioning (CF), Social Functioning (SF); and three symptoms scales: Fatigue (FA), Nausea and Vomiting (NV), Pain (PA). Additionally, this questionnaire includes a global health status/QoL scale and six single items: Dyspnoea (DY), Insomnia (SL), Appetite loss (AP), Constipation (CO), Diarrhoea (DI), Financial difficulties (FI). Higher score for functional scales represent higher level of functioning [24]. Informed consent was obtained from all patients.

Statistical analysis. Standard methods were used for descriptive statistics (mean, median, standard deviation). Differences between mean values of 2 or ≥3 groups were evaluated by the Student t-test, x^2 test and ANOVA. Pearson's and Speerman's correlation coefficients (r) were used to investigate the relationship between scales (HARS, HDRS, HRQoL scales) and main clinical and sociodemografic variables.

Results

One hundred and eight patients met the inclusion criteria, and eight of them refused to participate in the study. Detailed demographic and clinical characteristics of patients in our study were presented elsewhere [25]. The sample tended to be

Table 1 Scores of the Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) in the study participants

HARS		HDRS	
Score	Percent (%)	Score	Percent (%)
Without (0-9)	76	Without (0-7)	49
Mild (10-17)	22	Mild depression (8-13)	25
Mild to moderate (18-24)	2	Moderate (14-18)	19
Moderate to marked (25-31)	0	Marked (19-22)	5
Severe (>31)	0	Severe (>23)	2
Total number of patients	100	Total number of patients	100

Table 2 Relationships between Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) scores and selected demographic and clinical characteristics in the study participants

Variable	HARS		HDRS	
	Correlation coefficients (r)	P	Correlation coefficients (r)	P
Age	−0.088	0.385	−0.054	0.592
Disease duration	−0.038	0.709	−0.079	0.436
Education level	0.026	0.798	0.060	0.953
Occupation	−0.055	0.587	−0.095	0.346
Karnofsky index	−0.420	**0.001**	−0.487	**0.001**

middle-age (mean age at onset of disease was 58.5±8.3 years) and majority (71%) was male. The most patients (87%) had urban place of residence. Around half (48%) of the patients had 10-12 years of education (educational level equal to high school). The most were married (79%) and unemployed (69%) at the time of study enrolment. The majority had adeno-carcinoma (53%) and squamous cell carcinoma (40%). The average disease duration at the beginning of study was 5.4 ± 7.3 months. Karnofsky index was 80% in average. Sixty-six patients received chemotherapy (protocols: gemcitabine/cis(carbo)platin or cis(carbo)platin/etoposid) with or without radiotherapy which has been applied in 25 cases. Three patients received only palliative radiotherapy and 31 patients were enrolled before start of treatment. The average number of chemotherapy cycles was 4.0 ± 2.3. The most prominent side-effects of chemotherapy were nausea and vomiting present in 66.6% and 25.8% treated patients respectively.

Table 1 presents HARS and HDRS scores of study participants. The great majority of patients (76) had not symptom of anxiety but 24 patients demonstrated mostly mild anxiety symptoms. Around half (49%) of the patients did not show depressive symptoms. Mild depression was present in 25 patients, moderate in 19 patients and marked depression was evident in 5 participants. Only 2 patients scored in range of severe depression.

Scores obtained on HARS and HDRS were not correlated statistically significantly with age, disease duration, level of education and occupation profile (Table 2). Performance status (PS), measured on Karnofsky performance scale correlated significantly negatively with HARS and HDRS scores, i.e. patients with poor PS expressed significantly more anxiety and depressive symptoms (Table 2). Additionally, performance status correlated significantly positively with RE (r=0.264; p=0.008), MH (r=0.480; p=0.001), MCS (r=0.738; p=0.001) scales of the SF-36 questionnaire and EF scale (r=0.340; p=0.001) of the EORTC QLQ-C30.

The differences in HARS and HDRS scores according to the main demographic and clinical characteristics are presented in Table 3. The two genders did not differ in HARS and HDRS scores. In the present study, anxiety and depression were not

associated with age (≤60 vs. >60), place of living (urban vs. rural), marital status, presence of concomitant illnesses, stage of the disease (IIIB vs. IV), and treatment modality (HT vs. HT+RT). Statistically significant difference in scores of both HARS (p=0.029) and HDRS (p=0.002) was found only between employed and unemployed patients; unemployed patients had significantly less anxiety and depressive symptoms.

In the group of treated patients, statistically significantly better mental functioning measured by the SF-36 (MH scale) (p=0.011), as well as emotional functioning measured by EORTC QLQ C-30 (EF scale) (p=0.001) was observed. Also, treated patients expressed less anxiety and depressive symptoms comparing to newly diagnosed ones but these difference did not reach statistical significance. Additionally, unemployed patients scored significantly better in the mental health domain of SF-36 (MH, p=0.045; MCS, p=0.030) and the EF scale of EORTC QLQ C-30 (p=0.007) in comparison with employed patients.

The correlations between HARS and HDRS scores and side-effects of chemotherapy are shown on Table 4. There was statistically significant positive correlation between both HARS and HDRS scores and gastrointestinal toxicity. Furthermore, significant negative relationships were observed between presence of nausea and the following SF-36 scales: RE (r=-0.277; p=0.024), MH (r=-0.306; p=0.012) and MCS (r=-0.383; p=0.001), as well as the EF (r=-0.409; p=0.001) scale of the EORTC QLQ C-30. Presence of vomiting has shown significant negative correlation with RE (r=-0.311; p=0.011) scale and MCS (r=-0.296; p=0.016) of SF-36 and the EF (r=-0.309; p=0.012) of the EORTC QLQ C-30.

Discussion

Diagnosis of cancer is a stressful life event that often generates a great deal of fear and uncertainty. Therefore, symptoms of anxiety and depression and other forms of psychological distress are not surprising. It is well known that rates of distress often vary depending on age, sex and site of cancer [10, 26, 27]. On the other hand, many factors which can influence psychological distress in cancer patients are not fully elucidated. We

Table 3 Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) according to demographic and clinical characteristics in the study participants

Variable	HARS			HDRS		
	Mean score	SD	P	Mean score	SD	P
Gender						
– Male	6.01	5.08	0.965	8.14	6.34	0.596
– Female	5.96	4.75		8.93	7.56	
Current age						
– ≤ 60	6.39	4.76	0.324	8.57	6.43	0.706
– >60	5.38	5.27		8.05	7.21	
Place of residence						
– rural	6.08	5.44	0.953	9.46	6.87	0.532
– urban	5.99	4.92		8.21	6.71	
Employment						
– employed	7.61	4.86	**0.029**	11.48	7.95	**0.002**
– unemployed	5.27	4.87		6.97	5.60	
Marital status						
– married/cohabiting	5.86	4.95	0.589	8.07	6.80	0.398
– single/divorced/separated/widowed	6.52	5.11		9.48	6.39	
Concomitant illnesses						
– yes	6.11	4.67	0.810	9.15	6.25	0.218
– no	5.87	5.33		7.49	7.14	
Stage						
– IIIB	6.12	4.58	0.810	8.59	6.58	0.742
– IV	5.88	5.38		8.14	6.90	
Treatment						
– newly diagnosed	5.48	4.96	0.117	7.59	6.29	0.085
– chemotherapy ± radiotherapy	7.16	4.84		10.10	7.38	
Treatment modality						
– chemotherapy	5.56	5.40	0.543	7.48	6.40	0.750
– chemotherapy ± radiotherapy	4.75	3.78		6.95	5.54	
Number of chemotherapy cycles	5.51	5.20	0.597	7.53	6.31	0.636
– ≤ 4 cycles	4.76	4.26		6.70	5.66	
– > 4 cycles						

Table 4 Relationships between Hamilton Anxiety Rating Scale (HARS) and Hamilton Depression Rating Scale (HDRS) scores and toxicity induced by chemotherapy in the study participants

HT toxicity	HARS		HDRS	
	Correlation coefficient (r)	P	Correlation coefficient (r)	P
Anemia	-0.010	0.938	0.032	0.799
Leucopenia	0.078	0.534	0.071	0.571
Thrombocitopenia	-0.033	0.794	-0.024	0.848
Nausea	0.484	**0.001**	0.483	**0.001**
Vomiting	0.361	**0.003**	0.301	**0.014**
Alopecia	-0.107	0.395	-0.113	0.372

investigate the relationship between depression and anxiety symptoms and demographic, socioeconomic and clinical factors in patients with advanced NSCLC in Serbia.

In our study, around half of the patients (51%) expressed depressive symptoms by some extent and 25% of them demonstrated mild anxiety symptoms. Similar, significant level of anxiety and depressive symptoms has been found in other studies. Hopwood found a prevalence of self-reported depression and anxiety in NSCLC patients of 21% and 25% respectively [7]. Montazeri et al. reported that 23 % of patients with lung cancer were depressed and 16% were anxious [12]. In a more recent evaluation using Distress Thermometer (which has good reliability and is significantly correlated with the Hospital Anxiety and Depression Scale) anxiety symptoms were observed in 62.4% and depression symptoms in 49.3% patients [28].

Several studies demonstrated that younger patients and women report higher levels of psychological distress [10, 26, 29]. Also, in two studies using EORTC QLQ C-30 questionnaire, women reported poorer emotional functioning than men [30, 31]. We did not find significant influence of age and gender on psychological distress and emotional functioning, which is in accordance with several previous studies [4, 7, 12, 32]. In present study, no other sociodemographic (occupa-

tional profile, marital status, place of living) or clinical (disease duration, presence of concomitant illnesses, stage of the diseases, treatment modality) variables were related to anxiety and depressive symptoms. These findings are consistent with results from other studies in which demographic and clinical variables were unrelated to depression [10, 27, 28].

Our investigation demonstrated significant negative association between performance status and symptoms of anxiety and depression. Study conducted by Hopwood P. and Stephens R. also reported that performance status was independently associated with depression [7] Additionally, various studies have demonstrated a direct relationship between performance status and psychological domains of HRQoL in lung cancer patients [7, 33, 34]. Our study confirmed these results; we found that poor PS significantly negatively affects psychological domains of HRQoL measured by SF-36 and EORTC QLQ C-30.

The existing data about the lung cancer incidence points out significant association between lung cancer incidence and low educational, occupational and income-based socioeconomic position [35]. On the other hand, little is known about relationship between socioeconomic status of lung cancer patients and psychological distress (at initial presentation and during the treatment). Although not many, in the existing literature several study examined the effects of socioeconomic factors on HRQoL in cancer patients. Some of these studies have demonstrated significant relationship between lower socioeconomic status (assessed by different socioeconomic indicators) and worse HRQoL [36, 37]. In our survey, level of education and occupational profile did not influence on psychological wellbeing in patients with advanced lung cancer. In the study conducted by Uchitomi et al. among 212 lung cancer patients treated by curative resection, less well educated patients were at higher risk of depression [38]. One small study in Netherlands (n=99, mixed-site cancer patients) indicated that individuals with higher level of education had better emotional and physical wellbeing before their cancer diagnosis, but differences in emotional wellbeing disappeared at 2, 6 and 12 months post-diagnosis [39]. In contrast, in one previous study, when education was used as an indicator of socioeconomic status, higher education was found to be independent predictor of worse quality of life following treatment in prostate cancer patients [40]. Additionally, in our study, unemployed participants (which should implying low-income status) had significantly less symptoms of anxiety and depression compared to employed ones and scored significantly better in mental health domains of SF-36 (MH, MCS) and EF scale of EORTC QLQ C-30 questionnaire. These results are quite unusual, since several studies demonstrated an opposite results. In USA, the study comprised 1,173 men with newly diagnosed prostate cancer showed that lower annual income was independently associated with worse baseline HRQoL in all 8 SF-36 domains [37]. In one recent study, conducted in the United Kingdom among 352 patients with breast, prostate and colorectal cancer (socioeconomic status was indexed as

a composite of educational level, car and home ownership), patients with lower socioeconomic status were more anxious and depressed and had worse quality of life 2 months after diagnosis. In these patients psychological wellbeing improved 10 months after diagnosis. Furthermore, differences in psychological wellbeing between lower and higher socioeconomic groups were diminishing during this period [41]. Similar pattern, in terms of association between socioeconomic status and poorer quality of life immediately after diagnosis with a lack of association at follow-up, has been noted in several previous studies [37, 39, 42].

In our study sample unemployed patients possibly could have alternative source of income (black market) which is very difficult to examine. Possible explanation for unexpected better psychological wellbeing in unemployed patients could be in relation with this situation. Second, it is possible that employed patients faced to diagnosis of cancer which results in work disability have sense of a grater disruption of previous life-style then unemployed patients who are already adapted. Hence, financial circumstances may not have crucial impact on patient's psychological wellbeing as we expected, especially because in Serbia everyone has full health insurance coverage and access to health care is equal.

There is substantial evidence that palliative chemotherapy (active treatment in general) improve QoL in patients with advanced non-small cell lung cancer across broad spectrum of QoL domains (including psychological domain) and reduce symptom burden comparing to best supportive care [43, 44]. Results of our investigation are in accordance with these findings. Patients treated with chemotherapy had significantly better mental (SF-36) and emotional (EORTC QLQ C-30) functioning comparing to newly diagnosed patients. On the other hand, we did not find significant difference in frequency of anxiety and depressive symptoms between treated and newly diagnosed patients, although patients treated with chemotherapy experienced less anxiety and depressive symptoms during their illness. Similar results were obtained in one recent study conducted in Sweden among 159 patients with inoperable lung cancer who had completed the EORTC QLQ C30+LC13 at baseline (at diagnosis and before treatment), 1 month and 3 months later; emotional functioning was worst closest to diagnosis and improved during the treatment (31). This pattern may represent initial response to the cancer diagnosis as significant stressor, but also may reflect the positive influence of active treatment on long-term coping skills.

Patients entering cancer treatment consistently list chemotherapy-induced nausea and vomiting as one of their greatest fears [45]. Despite the progress in the field of emetic control, inadequately controlled nausea and vomiting remain a major problem [46]. Therefore, it is not surprising that gastrointestinal toxicity adversely affects many domains within patient's HRQoL [47, 48, 49]. Our results confirmed significant association between chemotherapy – induced nausea and vomiting and patients HRQoL. Moreover, besides negative influence on physical, functional and social domains and overall QoL, we observed

significant negative influence of nausea and vomiting over the mental and emotional domains as well. Additionally, patients with more severe nausea and vomiting reported significantly higher frequency of anxiety and depressive symptoms.

In conclusion, our study showed that psychological well-being of patients with advanced NSCLC, as well as presence of anxiety and depressive symptoms are considerably influenced by some disease – related factors (performans status, active treatment) and treatment – related factors (chemotherapy – induced nausea and vomiting). Additionally, our results impose precaution in the interpretation of the influence of socioeconomic factors on patient's psychological wellbeing because socioeconomic indicators may significantly differ within different society. Despite the nature of the advanced disease, patients should be routinely screened for both emotional and physical needs in order to develop appropriate interventions which should represent an essential part of palliative care.

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