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Health-related quality of life in different stages of breast cancer in Serbia

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Abstract. – OBJECTIVE: Breast cancer is the most commonly diagnosed malignant tumor worldwide, and Serbia ranks first in Europe in standardized breast cancer mortality rate. The aim of this research is to estimate health-related quality of life (HRQoL) and work productivity among patients in different stages of breast cancer in Serbia.

SUBJECTS AND METHODS: A total of 175 breast cancer patients attending the breast cancer outpatient clinic at the Oncology Institute of Vojvodina between March 2022 and February 2023 were included in the study. Patients were divided into three mutually exclusive groups: (1) First year after primary breast cancer (Group P), (2) Second and following years after primary breast cancer or recurrence (Group S) and (3) Metastatic disease (Group M). The EQ-5D-3L self-classifier was used to estimate the HRQoL, using the EQ-5D-3L index value and visual analog scale (VAS) score.

RESULTS: Mean EQ-5D-3L index value was 0.777 for Group P, and 0.768 for Group S. Patients with metastatic disease reported the lowest EQ-5D index value of 0.646 ($p < 0.05$). Pain/discomfort, as well as anxiety/depression, were the main drivers of the reduction in HRQoL. Patients in Group M also reported the lowest VAS score of 65.4. Furthermore, the highest percentage of women who sought leave or cited breast cancer as the reason for their early retirement were patients with metastatic disease.

CONCLUSIONS: HRQoL was most impaired in Group M, and patients with metastatic disease were more likely to take sick leave or retire early due to breast cancer. Delaying or preventing metastatic recurrence could significantly benefit patients' productivity and HRQoL.

Key Words:
Breast neoplasms, Neoplasm staging, Neoplasm metastasis, Quality of life, Serbia.

Introduction

According to the International Agency for Research on Cancer (IARC)[1], breast cancer is the most common malignant tumor worldwide, with 2.3 million new cases in 2020. Serbia has a high incidence rate of breast cancer (86.8/100,000 inhabitants), with over 4,600 new cases annually. Breast cancer is also the leading cause of cancer-related deaths among women, with 685,000 deaths globally in 2020[1]. Developing countries have a 17% higher mortality rate compared to developed countries[2], and Serbia ranks first in Europe in standardized breast cancer mortality rate (23.9/100,000)[1]. The premanifest phase of breast cancer development can last up to 10 years, providing sufficient time for secondary prevention[3]. Detecting breast cancer in the early stages allows for less invasive surgical methods, lower radiation doses, and significantly impacts treatment outcomes[4]. The five-year survival rate is 99% for localized disease compared to 29% for metastatic disease[5]. With the increasing variety of treatment strategies for breast cancer, the allocation of scarce healthcare resources to cost-effective treatments becomes more critical. Economic evaluations are performed to determine the cost-effectiveness of a treatment compared to a specific alternative. Health-Related Quality of Life (HRQoL) is a crucial factor in these evaluations and can significantly impact the results. As breast cancer predominantly affects working-age women, maintaining a high level of quality of life for patients is essential for their work productivity and has significant economic importance in addition to humanistic concerns[6]. HRQoL refers to the methods used to assess an individual's health status, values, attitudes, cognitive levels of satisfaction, and general well-being related to

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specific health conditions or life circumstances[7]. Generic and specific breast cancer questionnaires are used to evaluate HRQoL. Generic questionnaires, like the EQ-5D-3L, are advantageous in pharmacoeconomic evaluations as they offer a practical method for comparing quality of life across different disease stages and conditions[8]. Comprehensive studies[9-17] on the quality of life and the impact on work productivity at different stages of breast cancer have been conducted in many countries in Europe and around the world, while such research is scarce in Serbia. Therefore, the aim of this paper is to estimate HRQoL and work productivity associated with different stages of breast cancer in Serbia.

Subjects and Methods

Study Design

From March 2022 to February 2023, a naturalistic cross-sectional observational study was conducted at the Oncology Institute of Vojvodina on 185 female patients who had been previously diagnosed with breast cancer and attended an outpatient clinic. The study protocol has been approved by the Ethical Board of the Institute of Oncology of Vojvodina and the Ethics Committee for Clinical Trials of the Faculty of Medicine Novi Sad. Patients received all information and signed the informed consent before being included in the research. The study aimed to estimate HRQoL for patients at different stages of breast cancer during normal clinical practice without interfering with treatment. Patients were only included once, regardless of the number of times they attended the clinic during the recruitment period. The questionnaires collected demographic data, HRQoL, and work capacity information. Breast cancer disease state was determined based on epidemiological data from the Oncology Institute of Vojvodina, and 175 patients were eligible for analysis after excluding those with incomplete data. Patients were divided into three groups based on breast cancer disease: (1) first year after primary breast cancer (Group P), (2) second and following years after primary breast cancer or recurrence (Group S), and (3) metastatic disease (Group M). Patients in Group P had a primary breast cancer diagnosis within a year or less and no recurrence or metastatic disease. Group S included patients with a primary diagnosis or last recurrence more than 1 year prior to the questionnaire and non-metastatic disease. Group M comprised patients with at least one distant recurrence.

Health-Related Quality of Life

A standardized EQ-5D-3L questionnaire, consisting of two parts, was used to assess HRQoL. The first part included five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each with three levels of severity (no problems, moderate problems, or severe problems), providing a total of 243 possible health states. Based on a set of values for all possible health states, the health state was converted into a number called an index value[18]. Since there is no set of values for Serbia, the available set of values for Slovenia was used[19]. The second part of the questionnaire was a visual analog scale (VAS), presented as a vertical calibrated line ranging from 0 to 100, where 0 represented the worst imaginable health state. Patients were asked to mark a number on the provided scale to assess their current health state. The author's prior consent was obtained for the use of the Serbian language version.

Statistical Analysis

Statistical analysis was performed using the standard IBM SPSS Statistics v. 20 (IBM Corp., Armonk, NY, USA) and Microsoft Office Excel 2016 (Microsoft Corp., Redmond, WA, USA) packages. Numerical characteristics were presented as mean values, standard deviations (SD), and 95% confidence intervals, while categorical characteristics were presented as the percentage frequency of individual categories. The significance of differences in quality of life between the three breast cancer groups was first tested using the Kruskal-Wallis test. If a statistically significant difference was found, the Mann-Whitney U test was used to determine which groups showed a significant difference. The degree of correlation between the EQ-5D-3L index and VAS was assessed by determining the Pearson's coefficient. All analyses were evaluated at a significance level of $p < 0.05$. The results were presented both graphically and in tables.

Results

Patients' Characteristics

Table I presents data on patients' demographic characteristics, working status, and breast cancer state.

Table I. Patients' demographics.

Mean age (range)	62	(25-86)
Age distribution	**N**	**Percentage**
Less than 50	32	18%
50-64	71	41%
65 and older	72	41%
Total	175	100%
Education	**N**	**Percentage**
Elementary school	37	21%
High school	95	54%
University	32	18%
Other	11	6%
Total	175	100%
Working status	**N**	**Percentage**
Employed	40	23%
Unemployed	35	20%
Retired	100	57%
Total	175	100%
Breast cancer state	**N**	**Percentage**
Group P	55	31%
Group S	48	27%
Group M	72	41%
Total	175	100%

The average age of the patients was 62 (ranging from 25 to 86). More than half of the patients were under the age of 65. Most patients listed high school as the highest level of education (54%), while 32 women were college-educated (18%). Forty women were employed (23%), while 100 respondents (57%) were in retirement.

Compared to the defined stage of the disease, the largest number of patients belonged to Group M (41%). The year of primary diagnosis ranged from 1980 to 2022, with the majority of the patients having been diagnosed with breast cancer in 2020 or later.

Impact of Breast Cancer on Work Productivity

Out of 40 employed patients, 35 patients took sick leave in the previous three months due to breast cancer (88%), and the highest frequency of absenteeism was observed in Group M (93%). Furthermore, 31 patients retired early due to breast cancer (18%), with the most frequent occurrence being among patients with metastatic disease (31%).

Impact of Breast Cancer on HRQoL

The mean EQ-5D index values were: 0.777 [(95% confidence interval (CI): 0.726-0.829)] for Group P, and 0.768 (CI: 0.710-0.827) for Group S. Patients in Group M had the lowest mean EQ-5D index value of 0.646 (CI: 0.594-0.699) ($p < 0.001$) (Table II).

Patients with metastatic disease reported the greatest number of moderate or severe problems in all 5 dimensions. In Group P, problems related to self-care, normal activities, and anxiety/depression were more commonly reported compared to Group S (Figure 1).

The problems were most commonly related to pain/discomfort in 97 patients (55%) and anxiety/depression in 90 patients (51%). The fewest problems were reported in self-care, with 31 patients (18%). Problems related to usual activities were reported by 60 patients (34%), with this group having the most reported number of serious problems in 14 patients (8%). Mobility was a problem for 57 patients (33%) (Table III). A total of 46 patients (26.3%) reported a health condition without any problems in all five dimensions. The lowest percentage of such patients was in the Group M (16.7%).

Based on the VAS score, HRQoL was most impaired in Group M (VAS score of 65.4, CI: 60.4-70.5) and was statistically significantly different from Group P and Group S ($p < 0.05$). There were no statistically significant differences between Group P and Group S (Table IV).

Table II. EQ-5D-3L index value.

Group	Mean value	SD	95% CI
P	0.777	0.191	(0.726-0.829)
S	0.768	0.201	(0.710-0.827)
M	0.646	0.224	(0.594-0.699)

Significant difference between groups Kruskal-Wallis ($p = 0.0004$). Significant difference between Group P and Group M, Mann-Whitney U test ($p = 0.0003$). Significant difference between Group S and Group M, Mann-Whitney U test ($p = 0.003$).

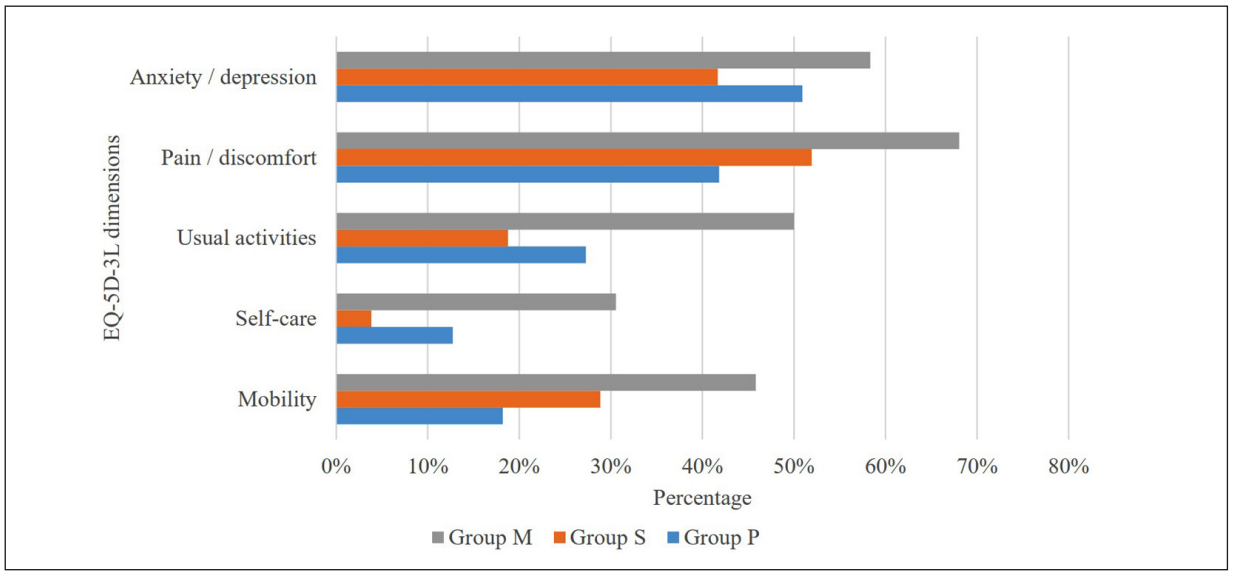

Figure 1. Percentage of patients reporting moderate or severe problems.

Table III. EQ-5D-3L dimensions.

Group	N	No problems		Moderate problems		Severe problems	
Mobility							
P	55	45	82%	9	16%	1	2%
S	48	34	71%	14	29%	0	0%
M	72	39	54%	29	40%	4	6%
	175	118	67%	52	30%	5	3%
Self-care							
P	55	48	87%	5	9%	2	4%
S	48	46	96%	1	2%	1	2%
M	72	50	69%	17	24%	5	7%
	175	144	82%	23	13%	8	5%
Usual activities							
P	55	40	73%	11	20%	4	7%
S	48	39	81%	9	19%	0	0%
M	72	36	50%	26	36%	10	14%
	175	115	66%	46	26%	14	8%
Pain/discomfort							
P	55	32	58%	23	42%	0	0%
S	48	23	48%	23	48%	2	4%
M	72	23	32%	43	60%	6	8%
	175	78	45%	89	51%	8	5%
Anxiety/depression							
P	55	27	49%	27	49%	1	2%
S	48	28	58%	16	33%	4	8%
M	72	30	42%	38	53%	4	6%
	175	85	49%	81	46%	9	5%

Table IV. EQ-5D-3L VAS score.

Group	Mean value	SD	95% CI
P	76.3	21.0	(70.6-81.9)
S	77.0	19.2	(71.4-82.5)
M	65.4	21.5	(60.4-70.5)

Significant difference between groups Kruskal-Wallis ($p = 0.002$). Significant difference between Group P and Group M, Mann-Whitney U test ($p = 0.0029$). Significant difference between Group S and Group M, Mann-Whitney U test ($p = 0.0034$).

There was a statistically significant correlation in all groups between the EQ-5D-3L index value and the VAS score ($p < 0.001$).

Discussion

Some articles[20-22] have mostly analyzed the impact of surgical interventions on the quality of life of breast cancer. Pekmezovic et al[23] conducted a study that compared the HRQoL of 100 female patients with breast cancer to a control group of 100 healthy women using a SF-36 questionnaire. Breast cancer patients scored lower compared to the healthy controls, with a statistically significant difference in terms of social and physical function. Furthermore, Novakov et al[24] investigated which group of factors (clinical, functional, psychological, or social) had the greatest influence on quality of life in women living with a breast cancer diagnosis. Their findings showed that psychological and social resources were more significant predictors of quality of life compared to clinical and functional factors.

Due to the substantial impact of breast cancer on both quality of life and work productivity, a thorough analysis of HRQoL was required at various stages of the disease.

The assessment of HRQoL methods represents an ongoing debate among experts. One part of the professional community advocates for the use of social tariffs, which are pre-prepared sets of values based on the health state of society as a whole, while others argue that only the patient can directly assess their individual state of health[25]. To consider both perspectives, we used the EQ-5D-3L, a standardized questionnaire consisting of two parts: the EQ-5D-3L index value and the VAS score[18]. Our study found a statistically significant correlation between the two methods of assessment. The results revealed that HRQoL is most affected in the metastatic stage of breast cancer, which is consistent with previous studies[11-17]. Lidgren et al[11] conducted a study in Sweden using the EQ-5D-3L questionnaire on a sample of 361 patients and found that the EQ-5D-3L index value in the metastatic group was 0.685. Pain/discomfort and anxiety/depression were the leading causes of impaired quality of life, coinciding with our research results. Verrill et al[13] used the EQ-5D-5L questionnaire with five dimensions and five gradation levels to investigate the quality of life at different stages of HER2-positive breast cancer in the UK. They calculated the EQ-5D-5L index of 0.695 in the metastatic group and the VAS score of 65.82, showing significant differences compared to groups with early breast cancer. In contrast to our findings, the most common quality of life problems in this study were related to self-care and usual activities. Studies conducted in Lithuania[12] and Brazil[15] using the EORTC QLQ-C30 specific questionnaire to examine the quality of life of breast cancer patients indicated that quality of life was significantly more impaired in the advanced stage of the disease in terms of the physical status of patients, primarily due to the present pain. However, unlike our study's results, there were no statistically significant differences in the emotional aspect. In addition, the authors of the study[17] conducted in the US concluded that quality of life is significantly impaired with more comorbidities, disease progression, and surgical complications, suggesting that future research should perform a more detailed analysis of the subgroups related to cancer type and therapeutic treatment[17]. Two review articles involving 75 studies in Latin America and the Caribbean[14] and 33 studies in Middle Eastern countries[16] also examined various factors affecting the quality of life of breast cancer patients and concluded that quality of life was most impaired in the advanced stage of the disease. Gonzalez et al[14] noted a significant difference in the quality of life not only in the metastatic cancer group but also in the group receiving active treatment that included surgical intervention, radiotherapy, or chemotherapy in the previous 6 months,

compared to patients in the continuous phase of treatment. In our study, there was no statistically significant difference between Group P and Group S. Patients in Group S reported more problems with mobility and pain compared to Group P. One of the reasons for such results may be a significantly higher average age of patients in Group S (65 years) compared to Group P (58 years). Patients in Group P reported problems with anxiety/depression in a much higher percentage, which is expected, given that they have recently been diagnosed with cancer and that it takes a long time for the person to process this information psychologically. El Haidari et al[16] conducted an analysis on the influence of socio-demographic and clinical factors on quality of life, revealing that individuals with higher education and employment status enjoy a better quality of life. Although our study did not explore the impact of socio-demographic factors on quality of life, it could serve as a suggestion for further research in this area.

Limitations

This study was conducted at a single center, and the participants came from the same geographical region. Also, our study only included patients who came for outpatient examination at the Oncology Clinic, which could have resulted in selection bias as the most severe cases that required inpatient treatment have not been included. The questionnaire did not gather information on marital status. The study did not collect data on past anti-cancer treatments; therefore, we were unable to analyze HRQoL based on different therapies. Despite these limitations, according to available literature, this is the first comprehensive study on the impact of different stages of breast cancer on quality of life and work productivity in Serbia and may serve as a basis for future research.

Conclusions

Patients suffering from metastatic breast cancer had the poorest HRQoL, based on both methods of assessment. The primary factors behind the negative effects on HRQoL were pain/discomfort and anxiety/depression. The highest percentage of women who took sick leave or cited breast cancer as the reason for their early retirement were patients with metastatic disease. The study findings suggest that delaying or preventing the metastatic recurrence of breast cancer, such as by prolonging the period of remission or detecting it at an early stage, could have broader advantages in terms of patient productivity and HRQoL.

Conflict of Interest

The authors declare that they have no conflict of interest to disclose.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Board of the Institute of Oncology of Vojvodina (21.11.2020/No. 4/20/2-3489/2-4), and the Ethics Committee of the Faculty of Medicine Novi Sad (18.12.2020/No. 01-39/298/1).

Informed Consent

All subjects provided written informed consent for inclusion before they participated in the study.

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Authors' Contributions

All authors contributed to the study's conception and design. Milica Paut Kusturica supervised the study. Marko Milovic wrote the first draft of the manuscript, and all authors commented on previous versions. All authors read and approved the final manuscript.

Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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