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PROGNOSTIC FACTOR OF BREAST CANCER AND COVID-19

Mirela Pirić, Enes Idrizović, Rifat Sejdinović, Edin Jusufović, Nehra Mosorović

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Mirela Pirić
Enes Idrizović
Rifat Sejdinović
Edin Jusufović
Nehra Mosorović

Affiliations:
1Public Health Health center of Brčko, Department of General Surgery, Brčko
2Health and Educational Institution Dr. Mustafa Šehović, Centre for Specific and Non-Specific Lung Diseases, Tuzla
3University in Tuzla, Faculty of Medicine, Tuzla
4University Clinical Center of Tuzla, Clinic for Surgery,Tuzla
5General Hospital Tešanj, Department of Internal Medicine. Tešanj
6University in Zenica, Faculty of Medicine, Zenica
7Health Medical Centre Lukavac, Departments for Occupational Medicine, Lukavac

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Corresponding author:
Mirela Piric, Public health institution Health center of Brčko, Department of General Surgery, Brčko
Email: mirela_piric@yahoo.com

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ABSTRACT

Background: Breast cancer is the most commonly diagnosed cancer in the world, and is the leading cause of death from cancer. The prognostic factors of breast cancer are lymph node status, tumour size, estrogen/progesterone receptor (ER/PR) status, histological grade, presence of lymphovascular invasion, Ki-67 proliferation index, age and ethnicity. The aim of the study was to determine the differences between prognostic factors of breast cancer before and during COVID-19 pandemic.
Patients and methods: This retrospective study covered the period March 2018-March 2022 and included 113 breast cancer patients from Brcko District. The patients were divided into two groups: before (n=66) and during the COVID-19 pandemic (n=47). The average age all patients was 61.99±12.15 years. The prognostic parameters of breast cancer (stage of the disease, menopausal status, histological type, histological grade, expression of Ki-67, tumour size, type of surgery, and axillary lymph node involvement) were analysed and compared between two groups.
Results: Higher histological grade of breast cancer and more frequent axillary lymph node involvement were observed during the pandemic.
Conclusion: COVID-19 pandemic resulted in more aggressive breast cancer.

Keywords: breast cancer, prognostic factors, COVID-19 pandemic.

INTRODUCTION

Breast cancer is the most common cancer in the world, with 2.3 million cases per year and the leading cause of cancer death in women. Globally, breast cancer is responsible for 684.996 deaths [1]. Based on the latest GLOBOCAN: Cancer Incidence, Mortality and Prevalence Worldwide report, 1.622 new cases of breast cancer could be expected annually in Bosnia and Herzegovina, with an incidence of 79.2 and an age-standardized incidence of 58.9[2].
Prognostic factors of breast cancer include tumour size, estrogen/progesterone receptor (ER/PR) status, histological grade, the presence of lymph node involvement, Ki67 proliferation index, age and ethnicity [3]. The two most important prognostic indicators for breast cancer are the size of the tumour and the degree of axillary lymph node involvement. Data on 24.740 cases recorded in the National Cancer Institute's Surveillance, Epidemiology and End Results Program (SEER) showed that survival rates varied from 45.5% for tumours with a diameter of ≥5 cm with positive axillary nodes to 96.3% for tumours <2 cm and without positive axillary nodes. It was found that tumour diameter and lymph node status act as independent prognostic indicators [4]. Furthermore, certain biological factors, including ER/PR and HER2 receptors, are both prognostic and predictive [3]. Ki-67 protein, usually detected immunohistochemically, is a cell marker of proliferation and reflects the aggressiveness of the breast cancer along with the response to treatment and the time of relapse [5]. On the other side, histological grade is also an important determinant of breast cancer prognosis and could be included in stage systems and algorithms for selecting the most appropriate treatment for breast cancer [3].
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was initially identified in patients in Wuhan, Hubei province, in December 2019 (6). In Bosnia and Herzegovina, the COVID-19 pandemic was declared on March 5, 2020 [7]. Worldwide data revealed a relative decline from 2019 to 2020 in breast cancer screening [8, 9].
This study was conducted with the purpose of understanding the prognostic

factors of breast cancer before and during the COVID-19 pandemic in Brcko District.

PATIENTS AND METHODS

This is a retrospective study conducted at General Hospital in Brcko District, where demographic, clinical and histopathological characteristics of tumours were taken from medical records in the period from March 2018 to March 2022.

113 operated patients with histologically pathologically proven breast cancer were included, in whom the suspected diagnosis was established earlier by radiological methods (mammography, ultrasound or magnetic resonance imaging) and after that confirmed by core biopsy before the operation. The age, gender, menopausal status of patients, as well as type of surgical procedure and three the most important prognostic factors (histologically grade, axillary lymph node involvement, and Ki-67) were analysed and compared between groups. Two patients with carcinoma in situ were excluded from the analysis of histological grade, lymph node involvement and Ki-67 expression.

Depending on the stage in patients with locally advanced disease, systemic therapy was carried out, followed by surgical treatment, while in early cancer some of the surgical treatments were carried out immediately. The exclusion factors were: patient's COVID-19 infection at the time of surgery, vaccination against COVID-19 and stage IV cancer of the disease, because these patients were treated in a reference centre and medical documentation was not available for them.

Ki-67 was painted according to protocols given by the American Association of Clinical Oncologists (ASCO) and the College of American Pathologists (CAP). These recommendations include minimizing the delay of prefixation, dividing surgical samples into slices of 5 to 10 mm for fixation, and fixation in neutral buffered formalin for 6-72 hours [10].

The study was approved by the ethics committee of general hospital of Brcko number: 05EO-002/12.

Statistical analysis was done with statistical programs SPSS version 24 and JASP version 0.16. Variables are represented visually (graphs and tables) and descriptive statistics (measures of central tendency and measures of variability) and inductive statistics (Student's T-test, Levin's F-test, $\chi 2$-square test) were performed. ANOVA test was used to calculate the relative difference of variance distribution between variables. Inductive statistics were made at a level of significance of 5% i.e. p-value <0.05 was considered statistically significant.

RESULTS

113 patients with breast cancer were included and divide in two groups: 66 (58.4%) patients before COVID-19and 47 (41.5%) patients in the COVID period.

The mean age of all patients was 61.99±12.5 years. Out of 113 patients, the female-male ratio was 112 (112 females and one male). Out of 112 female patients, there were significantly more patients in postmenopause (premenopausal *vs* postmenopausal): 13 (11.5%) *vs* 99 (89.61%); p<0.0001).

Table 1.Type of surgical procedures

Type of surgery	Before COVID-19	During-COVID-19	p value
Radical mastectomy	35 (53.03%)	29 (61.70%)	>0.05
Simplex mastectomy	4 (6.06%)	2 (4.26%)	>0.05
Partial breast resection with axillary dissection	17 (25.76%)	4 (8.51%)	>0.05
Partial breast resection with SLNB	8 (12.12%)	9 (19.15%)	>0.05
Partial breast resection	2 (3.03%)	3 (6.38%)	>0.05
Total	66 (100.00%)	47 (100.00%)	>0.05

Before and during COVID-19 similar frequency of different types of breast cancer surgery was observed (p>0.05) (Table 1).

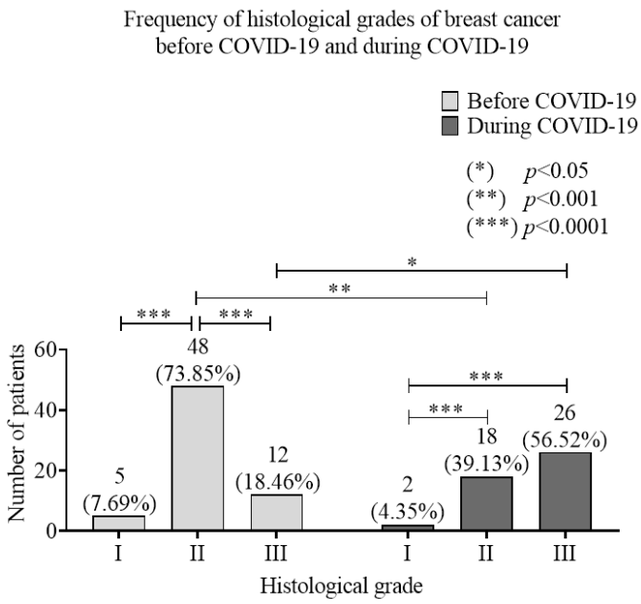

Figure 1. Frequency of histological grades in observed periods

In the period before COVID-19, the most common histological grade was II (p<0.0001), while in the period during COVID-19, the most common histological grades were II and III (p<0.0001). On the other hand, when the two groups were compared, grade III was more frequent during COVID-19(p<0.05), while grade II was more frequent before COVID-19 (p<0.001) (Figure 1).

Table 2. The number of removed and the number of metastatic axillary lymph nodes

Status of axillary lymph node	Before COVID-19	During COVID-19	p value
Axillary lymph nodes removed (median [min; max])	10 [6; 22]	12 [6; 19]	0.3565
Positive axillary lymph nodes (median [min; max])	0 [0; 10]	1 [0; 14]	0.04*

(*) The difference was statistically significant

Before and during COVID-19, surgically removed axillary lymph nodes were similar (p>0.05). However, during COVID-19, the number of axillary lymph nodes affected by breast cancer metastasis was higher compared to the period before COVID-19 (p<0.05) (Table 2).

Although the expression of Ki-67 before COVID-19 was higher than during the period during COVID-19, this difference did not reach statistical significance (p=0.05) (Figure 2).

DISCUSSION

In our study, prognostic factors of breast cancer were analysed before and during the COVID-19 pandemic. Several studies have reported increased morbidity and mortality of breast cancer during COVID-19 pandemic [11]. Our study also showed the negative effect of the COVID-19 pandemic on breast cancer. Therefore, the results of our study from this aspect were in agreement with literature data.

In the Turkish study of Ilgunet et al. showed that mastectomy rates remained similar with the pre-COVID-19 period [11]. However, multiple trials over the past few decades have led to the evolution from radical to less extreme breast preservation procedures. Mastectomy, which is a complete removal of the breast reserved for patients with locally advanced disease, for tumours larger than 5 cm, multicentre and multifocal breast cancer, inflammatory breast cancer, after sparing surgical treatment of breast cancer with positive resection margins or due to the occurrence of relapse [12]. Although our study showed that the number of operated patients during the COVID-19 pandemic was lower compared to the before pandemic

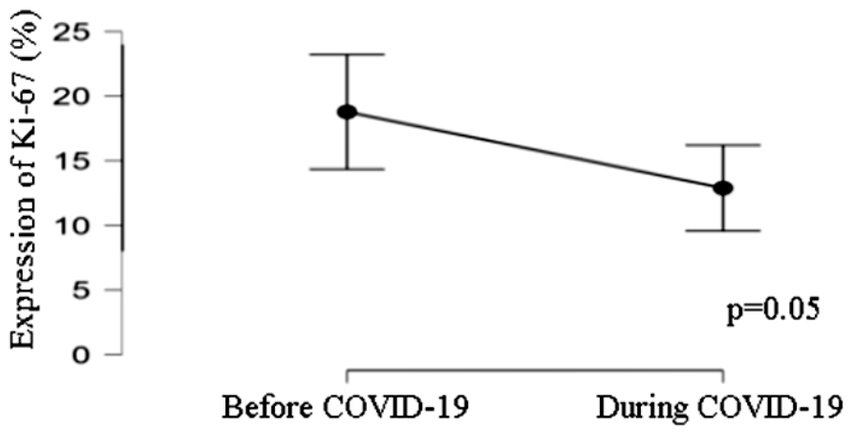

Figure 2. Expression of Ki-67 in the observed periods

period by 16.9%, we compared the type of surgery between these two periods. And found that patients before and during COVID-19 showed similar frequency of different types of breast cancer surgery. Our results were also in agreement with literature data.

A large study conducted by Henson and colleagues, estimating survival rates of 22.616 cases of breast cancer, showed that patients with histological grade 1, stage II had the same survival as those with stage 3 disease, stage I. The authors also found that patients with histological grade 1 tumours sized less than 2 cm had a very good prognosis, with 99% 5-year survival, even when they had positive lymph nodes [13]. These results are supported by the Nottingham Group, which included 2.219 operable cases of breast cancer with long-term follow-up. This study showed that histological degree was an important determinant of breast cancer outcomes and complementary to the state of the lymph nodes. This study provided evidence, hat the histological degree when used in combination with the involvement of the lymph nodes, histological degree showed a significant prognostic value [14]. In addition, a retrospective study conducted by Higgins and associates on the impact of the COVID-19 pandemic on breast cancer demonstrated a significant increase in the percentage of grade three tumours diagnosed in 2020 and a non-significant increase in 2021, with numbers in 2022 returning to 2019 levels [15]. A similar retrospective cohort study in Italy looking at both symptomatic and screen-detected cases surgically treated in one centre also found an increase in grades two and three tumours during the pandemic [16]. Our study showed that histological grades III of breast cancer was more frequent during COVID-19, but grade II was more common before COVID-19. Again, the results of our study from the aspect of histological grade are in agreement with literature data.

Lymph node involvement has long been recognized as an important prognostic factor of breast cancer. The presence of positive axillary lymph nodes is a predictor of an increased risk of local and distant relapse, which directly affects mortality [17]. Otherwise, the number of affected lymph nodes has traditionally been used to determine the stage of breast cancer. In addition, the ratio of lymph nodes, defined as the ratio of positive lymph nodes to the total number of lymph nodes removed, has emerged as a prognostic factor in an increasing number [18]. Besides a multicentre analysis of 432 patients conducted by Vanni at al. about delay in breast cancer treatments during the first COVID-19 lockdown reported an increase in lymph node involvement [19]. In our study, before and during COVID-19, surgically removed axillary lymph nodes were similar. However, our study showed that during COVID-19, the number of axillary lymph nodes affected by breast cancer metastasis was higher compared to the period before COVID-19.These results from our study are very similar to the results that got other authors.

A meta-analysis involving 12.155 patients showed that Ki-67 positivity gave a higher risk of recurrence and poorer survival rates in patients with early breast cancer. Although this meta-analysis could not examine whether Ki-67 had an independent prognostic value beyond standard clinical-pathological variables, it confirmed that high levels of Ki-67 were associated with poorer prognosis [20]. Another meta-analysis investigating markers of proliferation and survival in early breast cancer included data from 32.825 patients concluded that Ki-67 was associated with poorer survival rates [21]. Data reported at SABCS 2020 suggest that high levels of Ki-67 in combination with high-risk characteristics could be used to select patients who would benefit from the addition of abemacyclib to endocrine therapy in the treatment of ER positive, HER2-negative stage breast cancer I or II [22]. Adachi et al. in their research on delayed diagnosis and prognostic impact of breast cancer during the COVID-19 pandemic showed percentage of cases with a Ki-67 labelling index higher for 20 % in the pandemic group [23]. In our study although the expression of Ki-67 before COVID-19 was higher than during the period during COVID-19, this difference did not reach statistical significance. Analysing the results of other studies and our own, we can come to the conclusion the clinical benefit of Ki-67 as a prognostic marker could be more obvious if considered as part of a multiparameter biomarker panel.

Limitations of study

There were a few limitations to this study. Due to insufficient resources during the pandemic, other important prognostic factors of breast carcinoma, such as the expression of estrogen and progesterone receptors during the pandemic, were not investigated. This study is suggestive that the COVID-19 resulted in a possible delay of screening-based detection and consequently in more aggressive forms of breast cancer. Further researches are warranted to evaluate morbidity and mortality related to breast cancer and COVID-19.

Conflict of interest: none

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