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The modified Glasgow prognostic score (MGPS) and the mortality prediction model II (MPM II) can predict mortality in patients with breast cancer admitted to intensive care: A retrospective cohort study

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No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Breast cancer is the second most common cause of cancer-related death in women worldwide. Predicting the prognosis in breast cancer with very high mortality is important in terms of disease treatment and increasing life expectancy. In our study, we aimed to examine the importance of some inflammatory markers and scoring systems in predicting prognosis in patients with breast cancer who were hospitalized in the intensive care unit.

Methods: This retrospective cohort study was conducted in the Department of Medical Oncology and Intensive Care Unit between 2014 and 2020. Breast cancer patients who were admitted to the intensive care unit at any stage of their treatment during the study and followed up and treated in the medical oncology department of the hospital were included in the study. All data were compared between groups (discharged or exitus) based on survival status. Socio-demographic information, laboratory findings (hemoglobin, leukocytes, neutrophils, lymphocytes, platelets, eosinophils, monocytes, C-reactive protein [CRP], albumin, lactate dehydrogenase [LDH], clinical status [co-morbidities, length of stay in intensive care, mechanical ventilation, and reason for hospitalization in the intensive care unit]), and survival data of the patients were collected retrospectively from hospital medical records. We also recorded treatment-related data and relapse/progression information. Neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively) were calculated.

Results: Thirty-seven (52.1%) patients died and 34 (47.9%) patients survived. The NLR (P=0.021), Modified Glasgow Prognostic score (P<0.001), APACHE II score (P<0.001) and mortality probability model (MPM II) upon admission (P<0.001) were significantly higher in the exitus group than in the survivors. The lymphocyte_monocyte ratio (P=0.030) and prognostic nutritional index (P=0.004) were significantly higher in the discharged group than in the death group. When we evaluated performance of the prognostic scores to predict mortality, we found that the APACHE II score (area under the curve [AUC]: 0.939, 95% confidence interval [CI]: 0.888–0.990), MPM II-Admission (AUC: 0.936, 95% CI: 0.880–0.992), and modified Glasgow Prognostic Score ([mGPS] AUC: 0.727, 95% CI: 0.600–0.854) had the highest area under curve values. Multivariable regression revealed that longer chemotherapy duration (≥2 weeks), an mGPS score of two points, and high MPM-II (≥36 points) were independently associated with mortality.

Conclusion: Among the inflammatory markers and scores examined, mGPS and MPM-II were found to be independently associated with mortality in breast cancer patients who were hospitalized in the intensive care unit. In addition, patients with longer chemotherapy duration had a higher risk of mortality, but this result was limited by various possible confounders.

Keywords: intensive care unit, breast cancer, inflammation, clinical scoring, mortality

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Introduction

Breast cancer has become an increasingly important and preventable public health problem [1]. More than two million women worldwide were diagnosed with breast cancer in 2020. It is estimated that the cancer type with the highest prevalence in the last five years is breast cancer [2]. It is also the most common cancer in women in Turkey and constitutes 25% of all female cancers. [3].

Some risk factors for the development of breast cancer have been identified and include obesity, sedentary lifestyle, unhealthy diet, alcohol consumption, prolonged hormone replacement therapy, and various medications [4]. Although these factors may also affect the course of disease in those who are diagnosed with breast cancer, they have little role in quantifying the prognosis. Screening, preliminary treatments, and early diagnosis are critical for preventing breast cancer development and mortality; however, prediction of prognosis and survival in patients diagnosed with breast cancer is also a crucial matter to consider, particularly in relation with decisions regarding treatment [5]. It is known that inflammatory processes play an active role in the initiation, progression, and metastasis of cancer during almost all stages [6]. Based on these features, many studies have investigated the role of inflammation markers in predicting prognosis in different cancer types [7-9]. In studies concerning breast cancer, it was revealed that inflammatory parameters, such as the modified Glasgow Prognostic Score (mGPS), neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively), and Systemic Immune-Inflammation Index (SII) are associated with prognosis and mortality [10–14].

The number of studies investigating inflammatory markers has increased in recent years; however, the number of comprehensive studies, including scoring systems such as Prognostic Nutrition Index (PNI), Mortality Probability Models (MPM II), Acute Physiology and Chronic Health Assessment II (APACHE II), especially in hospitalized patients requiring intensive care, is still quite limited [15–17]. As such, no consensus on the use of clinical scoring and inflammatory markers in predicting breast cancer prognosis can be found. This study aimed to determine the role of inflammatory parameters in predicting mortality in breast cancer patients hospitalized in the intensive care unit (ICU).

Materials and methods

This retrospective cohort study was conducted in the Medical Oncology Department and Intensive Care Unit of Medipol University Faculty of Medicine between 2014 and 2020. Approval was obtained from the ethics committee of Medipol University for the study (Date: 18/11/2021, decision no: E-10840098-772.02-5922).

Study population

Patients with breast cancer who were admitted to the ICU at any stage of their treatment were included. Patients with systemic inflammatory disease in addition to breast cancer or with another malignancy at the same time were excluded from the study.

Laboratory and clinical records

Socio-demographic information, laboratory findings (hemoglobin, leukocytes, neutrophils, lymphocytes, platelets, eosinophils, monocytes, C-reactive protein [CRP], albumin, lactate dehydrogenase [LDH], clinical status [comorbidities, hospitalization duration in the ICU, mechanical ventilation, and reason for hospitalization in the ICU]), and survival data of the patients were collected retrospectively from the medical records. In addition, we recorded treatment-related data and recurrence/progression information. The NLR, PLR, and LMR were calculated by dividing the absolute values of the laboratory parameters.

Data collection and scoring tools

SII was obtained by multiplying the platelet count by the neutrophil count and dividing the obtained value by the lymphocyte count. A high value indicates a poor prognosis [19].

The PNI was obtained by multiplying the serum albumin (g/L) with the total lymphocyte count (10^9/L). Results are divided into two according to a threshold of 45, with higher values given a score of zero and lower values a score of [20]. Zero indicates normal, and 1 point indicates severe malnutrition. PNI has been shown to be an independent prognostic indicator in various cancers [21–23].

The MPM II is a prognostic scoring system that evaluates determinants thought to be effective in prognosis. Variables include the patient's level of consciousness, hospitalization in the ICU, malignancy, infection, cardio–pulmonary resuscitation, systolic arterial pressure, and age. For each variable, a score of zero or one is given based on presence/absence or threshold. Evaluation of MPM is done by probability calculation, which was independent of the total score [24]. Physiological variables evaluated in APACHE II include age, temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, venous HCO3, sodium, potassium, serum creatine, hematocrit, leukocytes, and Glasgow Coma Score (GCS). The highest value in the APACHE II score is 71 points, and mortality increases to 80% at 35 points and above [25].

Of the scores, MPM II was calculated upon the first admission of the patient to the ICU, while APACHE II was calculated after the patient completed the first 24 h in the ICU. All other laboratory values were obtained from the blood results at the initial ICU admission of the patient. Mortality was defined as the primary outcome for prognostic assessment.

High CRP (>10 mg/dL) and hypoalbuminemia (<3.5 mg/dL) were used to calculate mGPS [18]. Two points were given to those with two abnormalities, one point to those with one abnormality, and zero points if none were present. A high score indicated a poor prognostic indicator.

Statistical analysis

All analyses were performed on SPSS v25 (SPSS Inc., Chicago, IL, USA). Normality in continuous variables was checked using the Shapiro–Wilk test. According to these results, data concerning continuous variables were given as mean ± standard deviation or median (1^{st}–3^{rd} quartile), while categorical data were expressed as frequency and percentage values. Comparisons between the two groups were performed with either the independent samples t-test (when fulfilling parametric

assumptions), or the Mann–Whitney U test (non-parametric). Appropriate chi-squared tests were used to assess significance regarding categorical distributions. Prediction performances were evaluated by using a receiver operating characteristic (ROC) curve analysis by calculating the area under curve (AUC) and sensitivity and specificity values. Multiple logistic regression analysis (forward conditional method) was performed to identify the best prognostic factors influencing mortality. Finally, *P*-values of <0.05 were accepted as statistically significant.

Results

We evaluated 71 patients (70 females and one male) in our study. The median age was 58 (range 33–90) years. Thirty-seven (52.11%) patients died, and 34 (47.89%) were discharged.

The percentage of having undergone ≥4 weeks of chemotherapy was significantly higher in the exitus group than in the discharged group (*P*=0.003).

Neutrophil lymphocyte ratio (*P*=0.021), mGPS (*P*<0.001), APACHE II score (*P*<0.001), and MPM II upon admission (*P*<0.001) were significantly higher in patients who had died compared to survivors. The LMR (*P*=0.030) and prognostic nutritional index (*P*=0.004) were significantly higher in subjects who had been discharged compared to the exitus group. We found no significant differences between the groups in terms of PLR and SII index (Table 1).

In our study, APACHE II (94.59%), MPM II upon admission (89.19%), and mGPS (83.78%) were found to have the highest sensitivities in determining mortality. Specificity values were highest with the MPM II upon admission (84.85%), SII (79.41%), and APACHE II scores (78.79%). Curve analyses revealed that the highest AUC values were achieved based on the APACHE II score (AUC: 0.939, 95% confidence interval [CI]: 0.888–0.990), MPM II upon admission (AUC: 0.936, 95% CI 0.880–0.992), and mGPS (AUC: 0.727, 95% CI: 0.600–0.854) scores. The predictive performance of PLR and SII was not significant (Table 2, Figures 1 and 2).

According to multiple logistic regression analysis, we found long chemotherapy duration (≥2 weeks), an mGPS score of 2 points, and high MPM-II score (≥36) were independently associated with mortality (Table 3). Patients with an mGPS score of two points had a 19.694-fold higher risk of death (odds ratio [OR]: 19.694, 95% CI: 1.444–268.636; *P*=0.025). Patients with an MPM II (admission) score of ≥36 points had a 86.965-fold higher risk of death than those with lower scores (OR: 86.965, 95% CI: 6.930–1091.341; *P*=0.001). Other variables included in the model, including age (*P*=0.245), cancer status (*P*=0.716), reason for admission (*P*=0.107), NLR (*P*=0.400), PLR (*P*=0.388), LMR (*P*=0.929), SII (*P*=0.631), PNI (*P*=0.585), and APACHE II score (*P*=0.077) were found to be insignificant.

Table 3: Significant prognostic factors of the mortality, multiple logistic regression analysis

Prognostic Factors	B coefficient	*P*-value	OR	95.0% CI for OR	
Chemotherapy (≥2 weeks)	3.192	0.013	24.349	1.960	302.435
mGPS (2)	2.980	0.025	19.694	1.444	268.636
MPM II-Admission (≥36)	4.466	0.001	86.965	6.930	1091.341
(Constant)	-6.465	0.002	0.002		

Dependent Variable: Mortality, Nagelkerke R^2: 0.775, Correct prediction: 89.66%, OR: Odds ratio, CI: Confidence Interval, mGPS: Modified Glasgow prognostic score, MPM II: Mortality Probability Models

Figure 1: Receiver operating characteristic curve of the neutrophil–lymphocyte, platelet–lymphocyte, and lymphocyte–monocyte ratios (NLR, PLR, and LMR, respectively) and SII to predict mortality

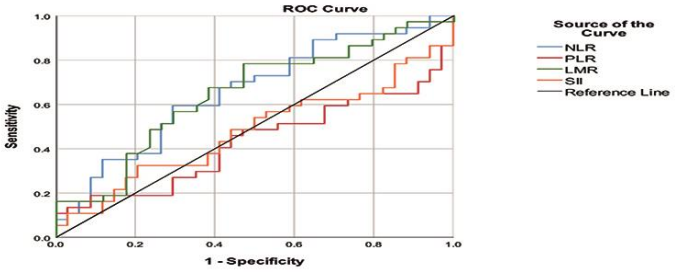
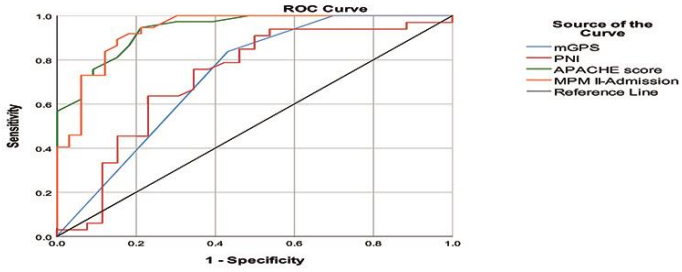


Figure 2: ROC curve of the modified Glasgow Prognostic Score (mGPS), Prognostic Nutritional Index (PNI), Acute Physiology and Chronic Health Assessment II (APACHE II) score, and Mortality Probability Models (MPM II)-Admission to predict mortality



Discussion

Breast cancer is the second most common cause of cancer-related deaths in women [26]. It is very valuable for clinicians to be able to predict the prognosis in cancer with such a high mortality. In this study, in which the significance of some inflammatory markers and scoring in predicting breast cancer prognosis was examined, higher mGPS score and MPM-II (≥36) were found to be associated with higher mortality. Moreover, having undergone chemotherapy for at least two weeks was associated with an increase in mortality.

It has been established that mGPS is an important inflammatory marker reflecting the prognostic status in breast and various other cancers. In this scoring system, albumin and CRP, which are biochemical tests that can be easily examined in blood, are evaluated in a combined way [18]. CRP, one of these components, is known to have a critical prognostic value as an inflammation marker in breast cancer patients [27]. Another component, hypoalbuminemia, may occur as a result of impaired nutrition secondary to an ongoing systemic inflammatory response [28]. Hypoalbuminemia has also been used to determine the prognosis of the disease in various cancer types [29,30]. The association of mGPS with poor clinical outcomes in patients with breast cancer was demonstrated in a study [31]. In addition, many studies have revealed that mGPS is associated with survival in other organ cancers [28,32–34]. In our study, mGPS was shown to be an important prognostic marker for mortality in breast cancer patients at the first admission in ICU. The mGPS values in our study were calculated from the blood taken at the time of a patient's first admission to the intensive care unit. When we look at the literature, no article reporting that the prognostic value of mGPS calculated at admission to the ICU in breast cancer patient is available. This lack of information should be viewed as important data that should be added to literature.

Table 1: Summary of patients characteristics and laboratory measurements with regard to groups

		Status		
Characteristics	**Total (n=71)**	**Exitus (n=37)**	**Discharged (n=34)**	***P*-value**
Age	58 (45–67)	58 (47–65)	55.5 (45–70)	0.982
Sex				
Female	70 (98.59%)	36 (97.30%)	34 (100.00%)	1.000
Male	1 (1.41%)	1 (2.70%)	0 (0.00%)	
Comorbidities	29 (40.85%)	14 (37.84%)	15 (44.12%)	0.767
Diabetes mellitus	11 (15.49%)	6 (16.22%)	5 (14.71%)	1.000
Hypertension	20 (28.17%)	10 (27.03%)	10 (29.41%)	1.000
Ischemic heart diseases	3 (4.23%)	2 (5.41%)	1 (2.94%)	1.000
COPD	2 (2.82%)	1 (2.70%)	1 (2.94%)	1.000
Hypothyroidism	3 (4.23%)	1 (2.70%)	2 (5.88%)	0.604
Atrial fibrillation	7 (9.86%)	3 (8.11%)	4 (11.76%)	0.703
Chronic renal failure	6 (8.45%)	2 (5.41%)	4 (11.76%)	0.417
Chemotherapy				
None	6 (8.57%)	2 (5.56%)	4 (11.76%)	0.003
< 2 weeks	22 (31.43%)	5 (13.89%)	17 (50.00%)	
2–4 weeks	6 (8.57%)	5 (13.89%)	1 (2.94%)	
> 4 weeks	36 (51.43%)	24 (66.67%)	12 (35.29%)	
Malignancy status				
Controlled / Remission	4 (5.63%)	1 (2.70%)	3 (8.82%)	0.024
Newly diagnosed	8 (11.27%)	1 (2.70%)	7 (20.59%)	
Recurrence / Progression	59 (83.10%)	35 (94.59%)	24 (70.59%)	
Stage				
Stage I	3 (6.38%)	1 (3.85%)	2 (9.52%)	0.717
Stage II	2 (4.26%)	1 (3.85%)	1 (4.76%)	
Stage III	0 (0.00%)	0 (0.00%)	0 (0.00%)	
Stage IV	42 (89.36%)	24 (92.31%)	18 (85.71%)	
Reason of ICU admission				
Respiratory problems	20 (28.17%)	11 (29.73%)	9 (26.47%)	0.002
Neurological problems	11 (15.49%)	7 (18.92%)	4 (11.76%)	
Sepsis	20 (28.17%)	15 (40.54%)	5 (14.71%)	
Postoperative	15 (21.13%)	1 (2.70%)	14 (41.18%)	
Others	5 (7.04%)	3 (8.11%)	2 (5.88%)	
Length of stay in ICU	3 (2–7)	5 (2–8)	2 (2–4)	0.010
MV	52 (73.24%)	36 (97.30%)	16 (47.06%)	<0.001
Invasive MV	34 (47.89%)	32 (86.49%)	2 (5.88%)	<0.001
Hemoglobin	10.77 (1.87)	10.65 (2.04)	10.91 (1.68)	0.553
Platelet (x1000)	146 (95–223)	105 (56 - 164)	219 (135–257)	<0.001
WBC	9360 (6240–14820)	9250 (6240 - 14820)	10685 (6410– 14150)	0.917
Neutrophil	7570 (5160–13000)	7430 (5340 - 13320)	7600 (5160– 11970)	0.917
Lymphocyte	610 (410 –1160)	530 (270–880)	735 (490–1640)	0.037
Eosinophil	10 (0–20)	0 (0 - 10)	15 (0–40)	0.011
Monocyte	410 (240–830)	480 (310–790)	370 (240–850)	0.604
CRP	85.63 (40.24–189.05)	118.28 (53.98– 198.84)	67.22 (5.35– 122.05)	0.030
Albumin	2.94 (0.67)	2.73 (0.56)	3.21 (0.72)	0.005
LDH	479 (285–782)	636 (285–1612)	439 (392–672)	0.755
NLR	11.41 (5.07–20.38)	14.71 (6.88–24.54)	8.09 (3.85–17.00)	0.021
PLR	218.03 (100.8–371.19)	192.16 (61.54–351.16)	218.67 (113.33– 390.24)	0.306
LMR	1.39 (0.75–2.71)	1.03 (0.70–1.70)	1.85 (0.98–3.56)	0.030
SII	1570.70 (556.07–3338.57)	1570.70 (334.15–3950.69)	1482.58 (646.19– 3138.67)	0.747
mGPS				
0	9 (13.43%)	0 (0.00%)	9 (30.00%)	<0.001
1	14 (20.90%)	6 (16.22%)	8 (26.67%)	
2	44 (65.67%)	31 (83.78%)	13 (43.33%)	
PNI	34.40 (28.75 - 40.65)	31.45 (27.85– 35.20)	38.15 (33.45 - 43.35)	0.004
APACHE II score	17 (11–27)	27 (19–32)	9 (7–14)	<0.001
MPM II-Admission	40.5 (23–77)	70 (49–92)	23 (8–26)	<0.001

Data are given as mean (standard deviation) or median (1st quartile-3rd quartile) for continuous variables according to normality of distribution and as frequency (percentage) for categorical variables. COPD: Chronic obstructive pulmonary disease, ICU: Intensive care unit, MV: Mechanical ventilation, WBC: White blood cell, CRP: C-Reactive protein, LDH: Lactate dehydrogenase, NLR: Neutrophil–lymphocyte ratio, PLR: Platelet–lymphocyte ratio, LMR: Lymphocyte–monocyte ratio, SII: Systemic immune-inflammation index, mGPS: Modified Glasgow prognostic score, PNI: Prognostic nutritional index; APACHE: Acute Physiology and Chronic Health Assessment II, MPM II: Mortality Probability Models

Table 2: Performance of prognostic scores for predicting mortality

Prognostic Scores	**Cut-off**	**Sensitivity**	**Specificity**	**Accuracy**	**PPV**	**NPV**	**AUC (95.0% CI)**	***P*-value**
NLR	≥12.6	59.46%	70.59%	64.79%	68.75%	61.54%	0.659 (0.532–0.786)	**0.021**
PLR	≥240	45.95%	55.88%	50.70%	53.13%	48.72%	0.429 (0.294–0.564)	0.306
LMR	<1.8	78.38%	52.94%	66.20%	64.44%	69.23%	0.649 (0.520–0.778)	**0.030**
SII	≥3200	32.43%	79.41%	54.93%	63.16%	51.92%	0.478 (0.342–0.614)	0.747
mGPS	2	83.78%	56.67%	71.64%	70.45%	73.91%	0.727 (0.600–0.854)	**0.002**
PNI	<35	72.73%	65.38%	69.49%	72.73%	65.38%	0.720 (0.581–0.859)	**0.004**
APACHE II score	≥15	94.59%	78.79%	87.14%	83.33%	92.86%	0.939 (0.888–0.990)	**<0.001**

MPM II is a prognostic scoring system used in ICU patients to predict mortality risk [35]. Most of the studies using MPM II were conducted to estimate the mortality of patients hospitalized in the ICU regardless of disease [24,36]. In a few studies conducted in cancer patients, it was shown that MPM II showed a performance than other scoring systems in predicting mortality [17,37]. Contrary to the literature, our study revealed that MPM II appears to be a significant prognostic marker in predicting the mortality of patients with breast cancer. Because the MPM II is calculated at the time of ICU admission, it mostly depends on the variables defined at the time of ICU admission or in the period immediately prior to admission. The most likely factor that could explain the conflicting results between our study and those in the literature may be the criteria for ICU admission. Differences in the admission criteria could be responsible for variations regarding patients' baseline characteristics, which could influence patient prognosis and treatment-related decisions, ultimately leading to considerable changes in outcome or other prognostic features.

In addition, inflammatory markers (NLR, PLR, LMR, SII) and scoring systems, such as PNI and APACHE II, were also examined to ascertain their value in predicting breast cancer prognosis in our study. Although different studies have shown that these markers and scoring systems have an important role in predicting breast cancer prognosis [12,16,38–41], in the multivariate analysis performed in our study, it was found that these parameters were not independently associated with breast cancer mortality. However, it should be noted that when sensitivity and specificity values were assessed, APACHE II score demonstrated relatively high values in both measures.

Another result of our study was that undergoing chemotherapy for a longer period of time was associated with increased risk of mortality and remained significant in multivariable analyses. This situation can be interpreted to be related to chemotherapy toxicity and side effects; however, it is evident that treatment decisions and length of therapy are based on relevant criteria, and therefore, these results should be evaluated cautiously and should not be generalized due to various biases and confounding factors that must be taken into account, including diagnosis, cancer stage, co-morbidities, planned duration of chemotherapy, and/or adjunct treatments. As such, it would be more appropriate to evaluate the effects of chemotherapy duration together with relevant factors, such as cancer type, time since diagnosis, chemotherapy protocol(s), last chemotherapy session, and patient-related characteristics.

Limitations

Our study has some limitations which include its single-centered, retrospective nature and small sample size. Since survival was defined as discharge from the ICU, longer-term survival data are not available and thus, detailed survival analyses could not be performed. In addition, data, such as time of diagnosis, chemotherapy protocol, time until chemotherapy initiation, use of additional treatments, and alternative therapies, were not assessed. These factors and various others may have affected prognosis. Our findings should therefore be interpreted cautiously and with these limitations in mind.

Conclusion

In this study, it was found that mGPS and MPM-II scores in breast cancer patients hospitalized in the intensive care unit were significant in determining mortality based on a multivariate analysis. Comprehensive, multicenter, prospective studies are needed to determine whether these parameters (or others) can be used to assess prognosis in breast cancer patients requiring intensive care during their treatment.

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