Creatine Kinase (CK)-MB and CK-MB-to-Total-CK Ratio: A Novel Predictive Marker for Pathologic Complete Response in Breast Cancer Treated with Neoadjuvant Chemotherapy

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ABSTRACT

Breast cancer is the most common cancer and neoadjuvant chemotherapy(NAC) is one of the important treatment modalities in early stage breast cancer. The aim of this study was to investi-gate the ability of serum CK-MB and CK-MB/CK to be an ideal predictive marker for pathologic complete response (pCR) in breast cancer patients receiving NAC and to determine its rela-tionship with clinico-pathologic factors. A total of 135 breast cancer patients receiving NAC were included in this retrospective study. The pre-NAC serum laboratory values and clinicopathologi-cal features of the patients were recorded. Regression analysis was used to do predictive factor analysis for pCR. In the statistical analysis, serum CK-MB level was associated with axillary status, PgR status, ER status, and HER2 status. A significant relationship between CK-MB/CK and axillary status and histological grade was found. PgR negativity, ER negativity, high histo-logical grade, axillary negativity, NLR, CK-MB elevation, and high CK-MB/CK ratio were found to be predictive factors for pCR in the univariate regression analysis.CK-MB (OR= 3.48, p= 0.032) and CK-MB/CK ratio (OR= 3.16, p= 0.028) were revealed to be strong predictors of pCR in established multivariate models.In survival analysis, recurrence-free survival (RFS) were shorter in patients with low CK-MB/CK ratio (p= 0.045). There was no significant relationship between CK-MB level and RFS (p= 0.315). In summary, in breast cancer patients who have re-ceived NAC, serum CK-MB level and CK-MB/CK ratio are independent predictors of pCR.To the best of our knowledge, this study is the first to assess these variables' predictive impact on NAC response in breast cancer patients.

Keywords: Breast cancer, Creatine kinase, CK-MB-to-total-CK ratio, Neoadjuvant chemotherapy, Predictive

INTRODUCTION

Excluding skin cancers, according to data for 2021, breast cancer is the most common cancer worldwide.[1] Breast cancer incidence is expected to rise further in future years, according to re-cent projections.[2] One of the preferred treatment methods for locally advanced breast cancer is neoadjuvant chemotherapy (NAC), which raises the probability that breast-conserving surgery can offer axillary downstaging and assess chemo-sensitivity before adjuvant treatment.[3,4] Patho-logical complete response (pCR) obtained after NAC has been demonstrated as a reliable prog-nostic marker for all breast cancer subtypes in large patient population studies and meta-analyses. Additionally, The United States Food and Drug Administration (FDA) recognized pCR as a reliable endpoint for neoadjuvant breast cancer research in 2018.[5-7] Current research was also designed in line with this.[8]

Previous research found imaging modalities, histopathological variables, genetic testing, and serum indicators to be predictive of pCR.[9-12] Serum markers are the most practical and readily available approach among these potential predictive parameters.

Creatine kinase (CK) is an en-zyme made up of B (Brain) and M (muscle) monomers that are expressed in a variety of tissues. It appears in serum as an isoenzyme in three different dimeric structures: CK-MB, CK-BB, and CK-MM.[13] CK-BB is primarily derived from the brain, lung, prostate, stomach, colon, and bladder, whereas CK-MM is derived from skeletal and cardiac muscle. The CK-MB isoenzyme is derived from heart muscle at a rate of 25%-46% and skeletal muscle at a rate of less than 5% in clinical applications. It is a significant marker utilized in the differential diagnosis of cardiac disorders, particularly acute coronary syndromes.[14-16]

Changes in serum CK-MB and CK levels have been reported to occur in several malignancies including breast cancer, although the mechanism behind these changes is not entirely under-stood.[17-19] In a large population cohort study conducted in China which included 88.415 patients, the CK-MB/CK ratio was found to be high in cancer patients and it was reported that it can be used in cancer screening.[17] Delahunt et al. reported that serum CK and CK-MB showed prognostic features in rhabdomyosarcoma patients.[20] Pan et al. reported that there is a correlation between CK level and cancer stage in breast cancer.[21] In addition, the relationship of CK-MB and CK with tumor cells has been demonstrated in many preclinical and cell line studies.[22-24]

Despite this malignancy-related feature studies investigating the relationship between CK-MB levels and CK-MB/CK ratio with chemotherapy response are lacking In this study, we aimed to investigate the ability of CK-MB and CK-MB/CK as a predictive marker for pCR, their prog-nostic properties and to determine their relationship with clinical and histopathological factors in breast cancer patients receiving NAC.

PATIENTS AND METHODS

Study Population

The study included outpatient breast cancer patients who received treatment between January 2018 and June 2021. The study included patients with 1) non-metastatic invasive breast cancer with pathological diagnosis; 2) 18 years of age or older; 3) those who received NAC and subsequently operated; 5) without concomitant skeletal muscle, brain-related disease, cardiac and renal dysfunction; 6) concomitant or no previ-ous history of malignancy; 7) no active infectious disease and no immunosuppressive drug use. All of the included patients received either docetaxel (75 mg/m^2) every 3 weeks for 4 cycles or paclitaxel (80 mg/m^2) once every 12 cycles after 4 cycles of cyclophosphamide (600 mg/m^2) and an anthracycline (epirubicin (100 mg/m^2) or doxorubicin (60 mg/m^2) combination. In the case of human epidermal growth factor receptor two positive (HER2+), patients received 4 cycles of trastuzumab (± pertuzumab) in the neoadjuvant period. Postoperative trastuzumab use was completed in one year in all HER2+ patients. Hormone receptor positive (HR+) patients were treated with hormone therapy after surgery and adjuvant radiotherapy was given to eligible patients in collaboration with a radiation oncologist.

Data Collection

The patient's demographic information, clinicopathological characteristics, and serum laboratory parameters measured before the first chemotherapy were recorded. In pathological evaluation, pCR was considered the absence of histopathological evidence of residual cancer cells in the breast and axillary lymph nodes.[25] In patients with a pCR response, pre-NAC histological type and molecular subtyping were accepted. According to the guide of the American Society of Clinical Oncology/College of American Pathologists, those with ER (estrogen receptor) and PgR (progesterone receptor) above 1% were considered positive.[26] Those who had a HER2 score of +3 after immunohistochemical (IHC) analysis and those who were +2 and positive by fluorescence in situ hybridization (FISH) analysis were considered HER2+. The pathology laboratory of our hospital reported the Ki-67 cutoff value as "18" for luminal separations, and this cut-off was used in the statistical analysis. Tumor pathological staging was performed according to the AJCC TNM classification.[27]

Following the potential predictor hypothesis based on CK-MB and CK-MB/CK factors, 641 patients with complete data who received NAC in our cent-

Tablo 1. Demographic and clinicopathological characteristics of the patients

Clinicopathological characteristics		Total n	%
Age	< 40 (Young Adult)	32	23.7
	≥ 40	103	76.3
BMI	< 25	45	33.3
	≥ 25	90	66.7
Menapause status			
Pre/Perimenopause		76	56.3
Postmenapause		59	43.7
Tumor size	≤ 2 cm	30	22.2
	> 2 cm	105	77.8
Axillary status	Negative	38	28.1
	Positive	97	71.9
Histologic type	Ductal	113	83.7
	Others	22	16.3
PgR status	Negative	62	45.9
	Positive	73	54.1
ER status	Negative	45	33.3
	Positive	90	66.7
HER2 status	Negative	96	71.1
	Positive	39	28.9
Ki-67	< 18	17	12.6
	≥ 18	118	87.4
Histologic Grade	Grade 1-2	58	43.0
	Gradde 3	77	57.0

BMI, Body-mass index; HER-2, Human epidermal growth factor receptor 2; ER, estrogene receptor; PgR, Progesterone receptor; pCR, Pathologic complet response.

er were examined. Patients whose CK and CK-MB levels were present within 1 week before the first chemotherapy were included in the study. A total of 144 patients were found to have CK and CK-MB laboratory parameters. Eight patients were excluded from the study because they could not complete the desired chemotherapy and due to unexpected findings in one patient's tests were considered to be of cardiac origin. The study was completed with 135 patients after these patients were removed.

CK-MB Measurements

In our hospital, biochemical tests are performed with Roche's Cobas 8000 c502 Analyzer (Roche Diagnostics; Geneva, Switzerland). Complete blood count data are determined using the ABX Pentra DX 120 (Horiba Medical, Montpellier, France) hematology analyzer.The CK Roche Cobas enzymatic UV method is used with the kit. It works with CK-MB Immunological UV test. The immunological approach used is that it inhibits the catalytic activity of CK-M sub-units in the immuno-inhibited sample without affecting the CK-B subunits, allowing CK-MB activity to be measured via CK-B activity.

Ethical approval was obtained from Tekirdag Namik Kemal University ethics committee (no: 2021.237.10.01 / October 26, 2021).

Statistical Analysis

Statistical analyzes were performed using SPSS Statistic software 24 (SPSS Inc., Chicago, III). Optimal cut-off values for CK-MB, CK-MB/CK, PLR (platelet to lymphocyte ratio), and NLR (neutrophil to lymphocyte ratio) were determined by the receiver operating characteristic (ROC) curve and the area under the curve (AUC). The median cut-off value was used for other labora-tory parameters. These cut-offs were used to differentiate the two groups as "low" and "high." The Fisher exact test and the Mantel–Haenszel chi-square test for trends were used to assess the association between categorical or ordinal variables and the presence of CK-MB and CK-MB/CK. Univariate and multivariate analyses were performed using the logistic regression model. To predict pCR, binary logistic regression using the "Forward: LR" method was used for multivariate analyses. Odds Ratio (OR) was reported with the corresponding 95% confidence intervals (95% CI). Times of recurrence-free survival (RFS) were calculated from date of initial surgery to date of first event or last follow-up (in cases without events). Survival analysis was performed using the Kaplan-Meier method and the Log-Rank test was used for group comparison.Statistical significance was accepted as $p< 0.05$.

RESULTS

Relationship Between Patient Characteristics and CK-MB and CK-MB/CK Ratio

A total of 135 patients were included in the study. They all consisted of women patients; the median age was 48 (range 23-78). The general characteristics of the patients are shown in Table 1.

Table 2. The relationship between patient features and the CK-MB and CK-MB/CK ratios

Clinicopathological characteristics	Low n (%)	CK-MB High n (%)		p	Low n (%)	CK-MB/CK High n (%)	p
Total	100 (74.1)	35 (25.9)			103 (76.3)	32 (23.7)	
Age	<40 (Young Adult)	27 (27)	5 (14.3)		25 (24.3)	7 (21.9)	
	≥ 40	73 (73)	30 (85.7)	0.128	78 (75.7)	25 (78.1)	0.781
BMI	< 25	33 (33)	12 (34.3)		30 (29.1)	15 (46.9)	
	≥ 25	67 (67)	23 (65.7)	0.890	73 (70.9)	17 (53.1)	0.063
Menapause Status							
Pre/Perimenopause	59 (59)	17 (48.6)			57 (55.3)	19 (59.4)	
Postmenapause	41 (41)	18 (51.4)	0.284		46 (44.7)	13 (40.6)	0.688
Tumor size	≤ 2cm	21 (21)	9 (25.7)		22 (21.4)	8 (25)	
	> 2cm	79 (79)	26 (74.3)	0.564	81 (78.6)	24 (75)	0.665
Axillary status	Negative	22 (22)	16 (45.7)		23 (22.3)	15 (46.9)	
	Positive	78 (78)	19 (54.3)	**0.007**	80 (77.7)	17 (53.1)	**0.007**
Histologic type	Ductal	85 (85)	28 (80)		85 (82.5)	28 (87.5)	
	Others	15 (15)	7 (20)	0.491	18 (17.5)	4 (12.5)	0.506
PgR status	Negative	40 (40)	22 (62.9)		45 (43.7)	17 (53.1)	
	Positive	60 (60)	13 (37.1)	**0.020**	58 (56.3)	15 (46.9)	0.349
ER status	Negative	27 (27)	18 (51.4)		31 (30.1)	14 (43.8)	
	Positive	73 (73)	17 (48.6)	**0.008**	72 (69.9)	18 (56.2)	0.152
HER2 status	Negative	76 (76)	20 (57.1)		76 (73.8)	20 (62.5)	
	Positive	24 (24)	15 (42.9)	**0.034**	27 (26.2)	12 (37.5)	0.219
Ki-67	< 18	12 (12)	5 (14.3)		13 (12.6)	4 (12.5)	
	≥ 18	88 (88)	30 (85.7)	0.769	90 (87.4)	28 (87.5)	1
Histologic Grade	Grade 1-2	44 (44)	14 (40)		50 (48.5)	8 (25)	
	Grade 3	56 (56)	21 (60)	0.681	53 (51.5)	24 (75)	**0.019**
Molecular Subtypes							
HR positive-HER2	Yes	56 (56)	9 (25.7)		53 (48.5)	12 (37.5)	
negative	No	44 (44)	26 (74.3)	**0.002**	50 (51.5)	20 (62.5)	0.168
HER2 positive	Yes	24 (24)	15 (42.9)		27 (26.2)	12 (37.5)	
	No	76 (76)	20 (57.1)	**0.034**	76 (73.8)	20 (62.5)	0.219
Triple negative	Yes	20 (20)	11 (68.6)		23 (22.3)	8 (25)	
	No	80 (80)	24 (31.4)	0.166	80 (77.7)	24 (75)	0.754

s Significant values are indicated in bold.
BMI= Body-mass index; CK-MB= Creatine kinase-MB; CK-MB/CK= Creatine kinase-MB to total creatine kinase ratio; HER-2= Human epidermal growth factor receptor 2; ER= Estrogene receptor; PgR= Progesterone receptor; HR= Hormone receptor

The CK-MB and CK-MB/CK cut-off values were determined using ROC-AUC curves. Cut-off values for CK-MB and CK-MB/CK were found 19.9 (AUC: 0.651, 95% CI: 0.55-0.76, p= 0.005) and 0.35 (AUC:0.633, 95% CI: 0.53-0.74, p= 0.013), respectively. According to the set cut-offs, 100 (74.1%) patients had low CK-MB, 35 (25.9%) patients had high CK-MB, 103 (76.3%) patients had low CK-MB/CK, and 32 (23.7%) patients had elevated CK-MB/CK. Serum CK-MB level was linked with axillary status (p= 0.007), PgR status (p= 0.020), ER status (p= 0.008), and HER2 status (p= 0.034), as indicated in Table 2. A significant relationship be-tween CK-MB/CK and axillary status (p= 0.007) and histological grade (p= 0.019) was found.

In the analysis performed according to the molecular subtypes of breast cancer, mean serum CK-MB

Tablo 3. Univariate analyses of factors for Pathologic Complete Response (pCR)

		Univariate analysis	
Variable	**Category**	**HR (95% CI)**	**P**
Clinicopathologic Characters			
Age	< 40/ ≥ 40	0.60 (0.26-1.37)	0.225
Menapos Status	Pre/Post	0.66 (0.32-1.42)	0.299
BMI	< 25/≥ 25	0.50 (0.23-1.06)	0.070
Histologic Type	Ductal/Others	1.27 (0.49-3.31)	0.620
PgR Status	Negative/Positive	0.20 (0.09-0.44)	**< 0.001**
ER Status	Negative/Positive	0.14 (0.06-0.32)	**< 0.001**
Ki67	< 18 / ≥ 18	2.39 (0.65-8.82)	0.190
HER2 Status	Negative/Positive	2.08 (0.96-4.52)	0.065
Grade	< 3/3	5.21 (2.18-12.44)	**< 0.001**
Tumor Size	< 2 cm / ≥ 2 cm	0.52 (0.23-1.21)	0.129
Axiller Status	Negative/Positive	0.10 (0.04-0.23)	**< 0.001**
Laboratory Parameters			
WBC (10^3/L)	< 6.6 / ≥ 6.6	0.80 (0.39-1.65)	0.540
Neu (10^3/µL)	< 3.93 / ≥ 3.93	0.53 (0.25-1.10)	0.087
Hgb (g/dL)	< 12.83/ ≥12.83	0.88 (0.42-1.81)	0.718
PLT (10^3/µL)	< 263/ ≥ 263	0.61 (0.29-1.26)	0.178
AST (U/L)	< 17/ ≥ 17	1.29 (0.62-2.69)	0.498
ALT(U/L)	< 15/ ≥ 15	1.03 (0.50-2.14)	0.938
Albumin (g/dL)	< 4.54/ ≥ 4.54	1.69 (0.80-3.54)	0.166
Protein (g/dL)	< 7.33/ ≥ 7.33	0.66 (0.30-1.46)	0.307
Na (mEq/L)	< 140/ ≥ 140	1.16 (0.51-2.63)	0.720
K (mmol/L)	< 4.42/ ≥ 4.42	1.36 (0.66-2.82)	0.405
Ca (mg/dL)	< 9.5/ ≥ 9.5	0.83 (0.40-1.71)	0.609
Creatinine (mg/dL)	< 0.65/ ≥ 0.65	1.07 (0.51-2.22)	0.860
CK (IU/L)	< 64/ ≥ 64	0.57 (0.28-1.20)	0.139
CK-MB (U/L)	< 19.9/ ≥ 19.9	4.46 (1.98-10.09)	**< 0.001**
NLR	< 2.09/ ≥ 2.09	0.40 (0.19-0.84)	**0.016**
PLR	< 136.85/ ≥ 136.85	0.58 (0.28-1.21)	0.147
GAR	< 0.61/ ≥ 0.61	1.25 (0.60-2.58)	0.551
CK-MB/CK	< 0.35/ ≥ 0.35	4.01 (1.75-9.21)	**0.001**
Deritis	< 1.07/ ≥ 1.07	1.05 (0.51-2.16)	0.900

s Significant values are indicated in bold.
WBC= White blood cell; Hgb= Hemoglobin; PLT= Platelet; NLR= Neutrophil to lymphocyte ratio; PLR= Platelet to lymphocyte ratio; GAR= Globulin to albumin raio; CK-MB= Creatine kinase-MB; Deritis= AST to ALT ratio; pCR= Pathologic complet response.

levels were significantly higher in the HER2+ molecular subtype (p= 0.034) and significantly lower in the HR+HER2-subtype (p= 0.002). There was no correlation observed between the CK-MB/CK ratio and molecular subtypes (Table 2)

Analysis of Predictive Factors for pCR

A logistic regression model was defined to determine predictive factors of pCR. PgR negativity (p= 0.001), ER negativity (p= 0.001), high histological grade (p= 0.001), axillary negativity (p= 0.001), NLR (p=0.016), CK-MB elevation (p= 0.001),

Tablo 4. Multivariate analyses of factors for Pathologic Complete Response (pCR)

	Model 1*		Model 2*	
Variable	**OR (95% CI)**	**P**	**OR (95% CI)**	**P**
ER Status	1.41 (1.06-1.94)	**< 0.001**	0.16 (0.06-0.42)	**< 0.001**
Axiller Status	0.13 (0.05-0.32)	**< 0.001**	0.13 (0.05-0.33)	**< 0.001**
CK-MB	3.48 (1.86-6.52)	**0.032**	-	-
CK-MB/CK	-	-	3.16 (1.13-8.81)	**0.028**

s Significant values are indicated in bold.
** Predictors (NLR, PgR status, grade, ER status, and axillary status) being significant in univari-ate analysis have been evaluated together with CK-MB and CK-MB/CK ratio in Model 1 and 2, respectively.*

and high CK-MB/CK ratio (p= 0.001) were found as predictive variables for pCR in the univariate analysis (Table 3). In the created model, CK-MB and CK-MB/CK predicted 71.9% and 71.1% of pa-tients with pCR, respective-ly.

To compare the predicted features in the univariate study, multivariate models were created. In Model-1, where CK-MB/CK was excluded and CK-MB was included, ER status (OR= 12.08, 95% CI: 5.11-28.56, p< 0.001) and axillary status (OR= 0.13, 95% CI: 0.05-0.32, p= 0.001) to-gether with CK-MB (OR= 3.48, 95% CI: 1.86-6.52, p= 0.032) were found independent predic-tive factors. In addition, ER status (OR= 0.16, 95% CI: 0.06-0.42, p= 0.001) and axillary status (OR= 0.13, 95% CI: 0.05-0.33, p0.001) continued to be predictive for pCR together with CK-MB/CK (OR= 3.16, 95% CI: 1.13-8.81, p= 0.028) in Model-2, which was established by excluding CK-MB and including CK-MB/CK. PgR and grade failed to show predictive properties in both models (Table 4).

Survival Analysis

Median follow-up was 44 months (range 9.8-98.8). During the follow-up period, recurrence (local or distant metastasis) occurred in 24 (17.8%) patients. The 4-year recurrence rates were found to be 17.6% for the high CK-MB group, 18% for the low CK-MB, 9.7% for the high CK-MB/CK and 20.4% for the low CK-MB/CK.

While mRFS was 59.6±5.8 months in patients with high serum CK-MB, it was 26±0.9 months in patients with low CK-MB. No significant survival difference was observed between the two patient groups (log-rank p= 0.315). mRFS was 65.9±5.3 months in patients with high serum CK-MB/CK ratio, and mRFS of patients with low CK-MB/CK ratio was 26±0.9 months. Poor overall survival was observed for patients with low CK-MB/CK ratio and Log-rank test showed that there was significant difference in overall survival between low CK-MB/CK and high CK-MB/CK patients (Log-rank p= 0.045) (Figure 1).

DISCUSSION

In our analysis, we investigated the relationship between serum CK-MB level and CK-MB/CK ratio with clinicopathological features and its predictive properties for pCR in breast cancer pa-tients receiving NAC. There was a statistical relationship between serum CK-MB level and HER2 status, axillary status, PgR status, and ER status, while CK-MB/CK ratio was related to axillary status, and histological grade. Both CK-MB and CK-MB/CK ratio were found to be predictive factors for pCR. Multivariate models were constructed to examine potential predictive factors for pCR. CK-MB, CK-MB/CK ratio, axillary lymph node status, and ER status present-ed independent predictive features. In addition, it was found that patients with high CK-MB/CK ratio had longer RFS, and serum CK-MB level had no effect on survival.

CK plays a crucial function in the intracellular ATP/ADP buffer in vertebrates and is a determining enzyme in energy hemostasis. Furthermore, it

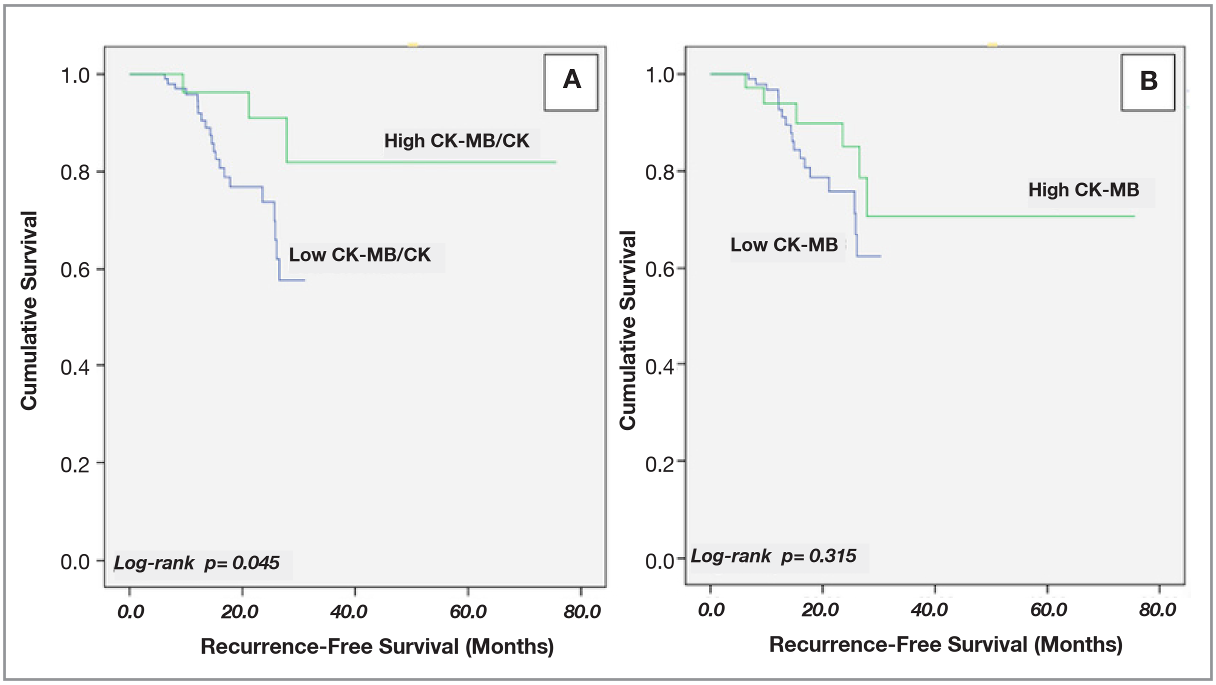

Figure 1. (A) Recurrence-free survival according to serum CK-MB levels, **(B)** Recurrence-free survival according to CK-MB/CK ratios

is considered that it may cause tumor cell de-velopment and progression by altering mitosis with the influence of CK-binding proteins.[22] In their study, Zhang et al. found that CK is an essential marker of congenital immunity and that its level may fluctuate as a defense mechanism against malignancies.[28] Serum CK levels were re-ported to be considerably lower in patients with breast cancer compared to the control group in a large case-control study by Pan et al., which included 823 patients with breast cancer and 1646 individuals. This finding was explained by low was linked to CK's immune reaction to the tumor.[21] However, as reported in these studies, there is no consensus on the prognostic properties of serum CK level despite its association with cancer and its mechanism is still unknown.[29-31] Although Yamazaki et al.[31] reported that CK was prognostic in gastric cancer and Murayama et al.[32] reported that CK was prognostic in esophageal cancer, this prognostic feature was not demon-strated in female patients in both studies. This suggests that CK has a close relationship with the hormonal system. Consistent with our study, in which only female patients were included, serum CK level alone was not found to be a predictive parameter of response to treatment; how-ever, when added to the CK-MB/CK ratio component of our new index, the new marker re-vealed both predictive and prognostic properties.

In our study, based on the immunoassay method applied in our center, the increase in CK-MB is thought to be due to an increase in CK-B monomer or an unexpected increase in CK-BB. Mooney et al. observed that an increase in CK-B, one of the CK monomers, promotes tumor proliferation in colon cancer during the G2/M phase of mitosis.[33] Furthermore, earlier research has shown that CK-B plays an active role in the immune system by activating and proliferating T cells during the immunological response and may promote progression by increasing intracel-lular energy generation.[23,24,28] This is supported by the limited number of studies showing that CK-MB/CK and CK-MB are increased in patients with metastatic cancer.[34,35] In a study involv-ing patients with neuroblastoma, high pretreatment CK-BB levels were reported to be a poor prognostic marker for overall survival.[36] Zarghami et al. reported that CK-BB was associated with aggressive histopathology, but the prognostic value of CK-BB level was limited.[37] In our study, no significant correlation was found between

CK-MB and survival time, but RFS was longer in patients with higher CK-MB/CK ratio. This result proves that the CK-MB/CK index is a more important prognostic factor. To the best of our knowledge, there are no studies on treat-ment response in the literature yet. However, studies on CK-MB monomers at the cellular level suggest an association between CK-MB and chemotherapy response, but further studies are needed.[38]

To the best of our knowledge this is the first study in literature reporting CK-MB and CK-MB/CK ratio as independent predictors of pCR in breast cancer patients receiving NAC. In the analysis performed to examine the relationship between the clinicopathological features of pa-tients and the CK-MB and the ratio of CK-MB/CK, it was found that the serum level CK-MB was significantly associated with axillary status, PgR status, ER status, and HER2 status and that the ratio CK-MB /CK was associated considerably with axillary status and histological grade. These factors associated with CK-MB and CK-MB/CK ratio have been reported as pre-dictive factors for pCR in previous studies.[39-41]

There are some limitations to our study. First, since it was a single-center study with small sam-ple size, precise assertions could not be used. Second, even if the patient selection criteria were carefully chosen, various circumstances can influence laboratory markers. Third, the mechanism and link between serum CK and CK-MB levels and breast cancer are unknown. Large-scale studies involving a large number of patients, both at the cellular and clinical level, are required to generalize the results.

Conclusion

In summary, our findings suggest that serum CK-MB levels and the CK-MB/CK ratio could be utilized as strong predictors of pCR in breast cancer patients receiving NAC. The use of these markers may have a decisive role in selecting patients who may benefit from NAC. Furthermore, additional research into our novel predictors may pave the road for possible therapeutic target therapies.

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