

# Utility of the CPS + EG score with real-life data in patients with breast cancer undergoing neoadjuvant chemotherapy

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**Abstract.** Breast cancer is the most common type of cancer in women, and predicting disease progression through CPS and EG scoring is important for treatment and prognosis, especially after neoadjuvant chemotherapy. The present study aimed to evaluate the association between the clinical and pathological stage (CPS) + estrogen receptor status and histologic grade (EG) score and disease-free survival (DFS) and overall survival (OS) in patients with breast cancer undergoing neoadjuvant chemotherapy. Data from 148 patients with breast cancer who were treated with neoadjuvant chemotherapy in the Medical Oncology Clinic of Izmir Tepecik Training and Research Hospital between 2013-2018 were analyzed. The following variables were assessed: Demographic characteristics, tumor size, clinical staging, estrogen receptor status, tumor nuclear grade in biopsy material and postoperative pathological staging. CPS + EG scores were calculated using simultaneous estrogen receptor status and tumor nuclear grade parameters, which were developed using the Neoadjuvant Therapy Outcomes Calculator Software of the MD Anderson Cancer Center. The 5-year OS and DFS rates were evaluated, and the 5-year follow-up of the patients was analyzed. The median follow-up period was 76.5 months, and the median survival time was 104.1 months. The pathological complete response (pCR) rate was 23.6%. Patients with a pCR were revealed to have a significantly higher DFS rate compared with the non-pCR group ( $P=0.038$ ). A significant decline in DFS was also demonstrated with increasing CPS + EG scores ( $P<0.001$ ). Moreover, a CPS score of 3-4 ( $P<0.001$ ) and a CPS + EG score of 3-4-5 ( $P<0.001$ ) were significantly associated with a worse OS. In conclusion, the relationship between the CPS + EG score and survival is apparent in the real-world

data in the present study. As the score increases, both the probability of recovery and OS decrease. Furthermore, the CPS + EG scoring system is an easy, free and accessible method to estimate prognosis.

## Introduction

Breast cancer continues to be the most common cancer and a leading cause of mortality among women (1). A total of >2 million women are diagnosed with breast cancer globally per year (2) and predicting disease progression has become a central focus in cancer research (3). Furthermore, it is of great importance to determine the stage of breast cancer at the first presentation and enable the treatment plan and the prediction of cancer prognosis (4).

The diagnosis of invasive breast cancer requires the evaluation of estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, the tumor proliferation index (Ki-67), lymphatic and vascular invasion status and tumor oncogenesis of the biopsy specimen. Tumor-node-metastasis (TNM) staging provides a universal language for clinicians with a collective approach and interpretation regarding prognosis, and currently, the 8th edition of the American Joint Cancer Committee is used for breast cancer staging (5). PR status may be disregarded as a predictive factor if the ER status is noted to be positive (6). Another parameter considered in the histopathological examination is tumor grade, which evaluates tubule formation, nuclear polymorphism and mitotic activity together. Elston *et al* (7) reported that tumors with higher tumor grades were associated with worse clinical outcomes. This was further validated by Rakha *et al* (8). Taken together, a prognostic model was created with a scoring system based on these clinicopathological parameters. Using the Neoadjuvant Therapy Outcomes Calculator software, developed at the MD Anderson Cancer Center, the pretreatment clinical stage and post-treatment pathologic stage, as well as ER status and tumor nuclear grade, are incorporated to assess the prognosis and survival rates of patients with breast cancer treated with neoadjuvant chemotherapy (NACT) (9,10). This prediction model indicates that high score rates are associated with poor prognosis.

The present study aimed to assess the association between clinical and pathological stage (CPS) and ER status and histologic grade (EG) scoring with disease-free survival (DFS)

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and overall survival (OS) in patients with breast cancer who are treated with NACT in a Turkish population. Treatment outcomes were not included as this would require a large-scale randomized controlled study. The evaluation of the CPS + EG scoring system in this population group has not been studied yet in Turkey, to the best of our knowledge.

## Materials and methods

The present retrospective study included data from 148 patients diagnosed with breast cancer who were treated with neoadjuvant systemic chemotherapy followed by surgery in the Medical Oncology Clinic of Izmir Tepecik Training and Research Hospital (Bornova, Turkey) between 2013 and 2018. The patients included had a histopathologically confirmed diagnosis of breast cancer, were at clinical stage II or III (5), and received neoadjuvant systemic therapy (chemotherapy and/or anti-HER2 therapy). Patients with distant metastasis at the time of diagnosis and patients with any secondary malignancies were excluded from the analysis. Ethics approval for the present study was obtained from the local ethics committee of Izmir Tepecik Education and Research Hospital (approval no. 2023/08).

The following variables were analyzed: Demographic characteristics, tumor size at presentation, clinical staging with lymph node involvement and distant metastasis status (clinical TNM stage), ER status and tumor nuclear grade (NG) in biopsy material, and postoperative pathological staging after NACT [namely, pathological TNM stage after treatment (ypTNM)]. Postoperative tumor pathological response grading was categorized as progression, stable response, partial response and complete response (CR) to treatment. A pathological (p)CR was defined as the presence of residual ductal carcinoma *in situ* in the breast (ypTisN0) or the absence of an invasive tumor in both the breast and axillary lymph nodes (ypT0N0). CPS scores were calculated using the clinical stage at presentation and pathological stage after NACT. CPS + EG scores were calculated using the simultaneous ER status and NG, as implemented in the Neoadjuvant Therapy Outcomes Calculator Software of the MD Anderson Cancer Center (5,6). As the CPS-score 4 group included only 1 patient, this was excluded from the analysis. The scoring criteria for each parameter are presented in Table I. The 5-year OS and DFS expectations were recorded as percentages and the 5-year follow-up of the patients was analyzed.

The distribution of continuous variables was assessed for normality using the Kolmogorov-Smirnov test and skewness and kurtosis. Categorical variables are presented as n (%), whilst continuous variables are reported as mean  $\pm$  standard deviation or median (interquartile range). OS was defined as the time from disease diagnosis to death, and DFS was defined as the time from diagnosis to relapse. Statistical calculations were performed accordingly. OS and DFS were evaluated using the Kaplan-Meier method. The log-rank test was used to determine differences in survival. Median follow-up time was calculated using the reverse Kaplan-Meier method. Univariate and multivariate Cox proportional regression models were used to identify predictive variables for survival. SPSS v29.0 (IBM Corp.) and JAMOV v2.6.2 ([www.jamovi.org](http://www.jamovi.org)) were used for statistical analyses.  $P < 0.05$  was considered to indicate

a statistically significant difference. However, in univariate analyses,  $P < 0.10$  was considered for inclusion of a variable in the multivariate model for further analysis. The analysis was computed using the backward elimination likelihood ratio method.

## Results

**Patient characteristics and follow-up.** A total of 148 female patients were included in the present study, with a mean age of  $49.3 \pm 10.0$  years. The clinicopathological characteristics of patients are presented in Table II. The median follow-up period was 76.5 months [95% confidence interval (CI), 67.7-85.4]. The median OS was 104.1 months (95% CI, 97.4-110.9). The median DFS was 96.0 months (95% CI, 88.5-104.5). The overall pCR rate was 23.6%.

**Survival and treatment response based on CPS and CPS+EG scores.** Treatment responses based on CPS and CPS + EG scoring are presented in Tables III and IV, respectively. OS and DFS analyses were performed by stratifying patients into five (0-1-2-3-4) groups based on CPS scores. A significant decrease in OS was observed as CPS and DFS scores increased (both  $P < 0.001$ ; Figs. 1 and 2; Table V). 5-year OS and PFS rates of 46, 80, 95 and 100%, and 40, 69.5, 95 and 100%, respectively, were calculated for CPS scores of 3, 2, 1 and 0, respectively. Similarly, OS and DFS analyses stratified by CPS + EG scores (0-1-2-3-4-5-6) demonstrated a significant decrease in OS and DFS as scores increased (both  $P < 0.001$ ; Figs. 3 and 4; Table V). Patients with a pCR demonstrated significantly higher DFS rates compared with that of non-pCR ( $P = 0.038$ ). Moreover, a CPS score of 3-4 (in comparison with 0-1-2) and a CPS + EG score 3-4-5 (in comparison with 0-1-2) were significantly associated with a worse OS (both  $P < 0.001$ ; Figs. 1 and 3, Table V).

**Recurrence.** Patients with recurrence had a shorter median OS (median, 64.3 months; 95% CI, 52.8-75.8) than patients without recurrence (median, 118.4 months; 95% CI, 113.5-123.3) ( $P < 0.001$ ). When patients were stratified according to their pCR status, median DFS and median OS was significantly lower in patients with recurrence ( $P = 0.013$  and  $P = 0.038$ , respectively; Figs. 5 and 6, Table V).

**HER2 status.** OS was also significantly higher in HER2-positive patients compared with HER2-negative patients ( $P = 0.015$ ; Fig. 7). Furthermore, DFS was significantly higher in HER2-positive patients compared with HER2-negative patients ( $P = 0.021$ ; Fig. 8). Moreover, the 5-year OS rates for HER2-positive and -negative patients was 86 and 74%, respectively, whereas the 5-year PFS was 84 and 66%, respectively.

**Univariate and Cox regression analysis.** Univariate analyses of the variables are presented in Table V. Cox regression analysis revealed that HER2-negative status and higher CPS scores (3-4) were significantly associated with worse OS and DFS rates. HER2-negative patients had a higher risk of mortality [hazard ratio (HR), 2.447;  $P = 0.038$ ] and recurrence (HR, 2.203;  $P = 0.033$ ) compared with HER2-positive

Table I. Points given to each variable in the clinical and pathological stage + estrogen receptor status and histologic grade scoring system.

| Variable                 | Points |
|--------------------------|--------|
| Clinical stage (cAJCC)   |        |
| I                        | 0      |
| IIA                      | 0      |
| IIB                      | 1      |
| IIIA                     | 1      |
| IIIB                     | 2      |
| IIIC                     | 2      |
| Tumor marker             |        |
| ER negative              | 1      |
| Pathologic stage (pAJCC) |        |
| I                        | 0      |
| IIA                      | 1      |
| IIB                      | 1      |
| IIIA                     | 1      |
| IIIB                     | 1      |
| IIIC                     | 2      |
| Nuclear grade            |        |
| 3                        | 1      |

AJCC, American Joint Committee on Cancer; cAJCC, clinical AJCC stage; ER, estrogen receptor; pAJCC, pathological AJCC stage.

Table II. Clinicopathological characteristics of the patients in the present study.

| Variable           | Total (n=148) |
|--------------------|---------------|
| Age, years         | 49.3±10.0     |
| Pathological LNs   | 1 (0-3)       |
| Survival           |               |
| Dead               | 38 (25.7)     |
| Survived           | 110 (74.3)    |
| Hormone status     |               |
| Positive           | 102 (68.9)    |
| Negative           | 46 (31.1)     |
| HER2 status        |               |
| Negative           | 87 (58.8)     |
| Positive           | 61 (41.2)     |
| Menopause status   |               |
| Premenopausal      | 71 (48.0)     |
| Perimenopausal     | 12 (8.1)      |
| Postmenopausal     | 64 (43.2)     |
| Unknown            | 1 (0.7)       |
| Pathological stage |               |
| 0                  | 34 (23.0)     |
| 1                  | 25 (16.9)     |
| 2A                 | 39 (26.4)     |
| 2B                 | 10 (6.8)      |

Table II. Continued.

| Variable                    | Total (n=148) |
|-----------------------------|---------------|
| 3A                          | 24 (16.2)     |
| 3B                          | 10 (6.8)      |
| 3C                          | 6 (4.1)       |
| CPS score                   |               |
| 0                           | 8 (5.4)       |
| 1                           | 42 (28.4)     |
| 2                           | 67 (45.3)     |
| 3                           | 30 (20.3)     |
| 4                           | 1 (0.7)       |
| Tumor diameter, mm          | 15.5±21.9     |
| Operation                   |               |
| Lumpectomy                  | 19 (12.8)     |
| Mastectomy                  | 129 (87.2)    |
| Relapse                     |               |
| Yes                         | 42 (28.4)     |
| No                          | 106 (71.6)    |
| Triple-negative             |               |
| Yes                         | 22 (14.9)     |
| No                          | 126 (85.1)    |
| Adjuvant RT                 |               |
| Received                    | 147 (99.3)    |
| Unknown                     | 1 (0.7)       |
| Lymph nodes at the diagnose |               |
| Absent                      | 7 (4.7)       |
| Mobile LN                   | 102 (68.9)    |
| Fixed LN                    | 31 (20.9)     |
| Others                      | 8 (5.5)       |
| Clinical response           |               |
| PD                          | 12 (8.1)      |
| PR                          | 94 (63.5)     |
| CR                          | 35 (23.6)     |
| SD                          | 7 (4.7)       |
| CPS + EG score              |               |
| 0                           | 3 (2.0)       |
| 1                           | 22 (14.9)     |
| 2                           | 39 (26.4)     |
| 3                           | 49 (33.1)     |
| 4                           | 28 (18.9)     |
| 5                           | 7 (4.7)       |

Data are presented as mean ± standard deviation, median (interquartile range) or n (%). LN, lymph node; HER2, human epidermal growth factor receptor 2; CPS, clinical and pathological stage; RT, radiotherapy; PD, progressive disease; PR, partial response; CR, complete response; SD, stable disease; EG, estrogen receptor status and histologic grade.

patients. Similarly, patients with higher CPS scores had a significantly increased risk of poor OS (HR, 5.111; P=0.007) and DFS (HR, 3.876; P=0.025). Furthermore, a higher CPS +

Table III. Distribution of clinical and pathological stage scores according to responses.

| Response          | CPS score |           |           |           |         |
|-------------------|-----------|-----------|-----------|-----------|---------|
|                   | 0         | 1         | 2         | 3         | 4       |
| Progression       | 0 (0.0)   | 1 (8.3)   | 7 (58.3)  | 4 (33.3)  | 0 (0.0) |
| Partial response  | 3 (3.2)   | 21 (22.3) | 46 (48.9) | 23 (24.5) | 1 (1.1) |
| Complete response | 5 (14.3)  | 20 (57.1) | 10 (28.6) | 0 (0)     | 0 (0.0) |
| Stable disease    | 0 (0.0)   | 0 (0.0)   | 4 (57.1)  | 3 (42.9)  | 0 (0.0) |

Data are presented as n (%). CPS, clinical and pathological stage.

Table IV. Distribution of clinical and pathological stage + estrogen receptor status and histologic grade scores according to responses.

| Response          | CPS + EG score |           |           |           |           |         |
|-------------------|----------------|-----------|-----------|-----------|-----------|---------|
|                   | 0              | 1         | 2         | 3         | 4         | 5       |
| Progression       | 0 (0.0)        | 1 (8.3)   | 5 (41.7)  | 1 (8.3)   | 5 (41.7)  | 0 (0.0) |
| Partial response  | 1 (1.1)        | 12 (12.8) | 24 (25.5) | 32 (34.0) | 18 (19.1) | 7 (7.4) |
| Complete response | 2 (5.7)        | 9 (25.7)  | 9 (25.7)  | 12 (34.3) | 3 (8.6)   | 0 (0.0) |
| Stable disease    | 0 (0.0)        | 0 (0.0)   | 1 (14.3)  | 4 (57.1)  | 2 (28.6)  | 0 (0.0) |

Data are presented as n (%). CPS, clinical and pathological stage; EG, estrogen receptor status and histologic grade.

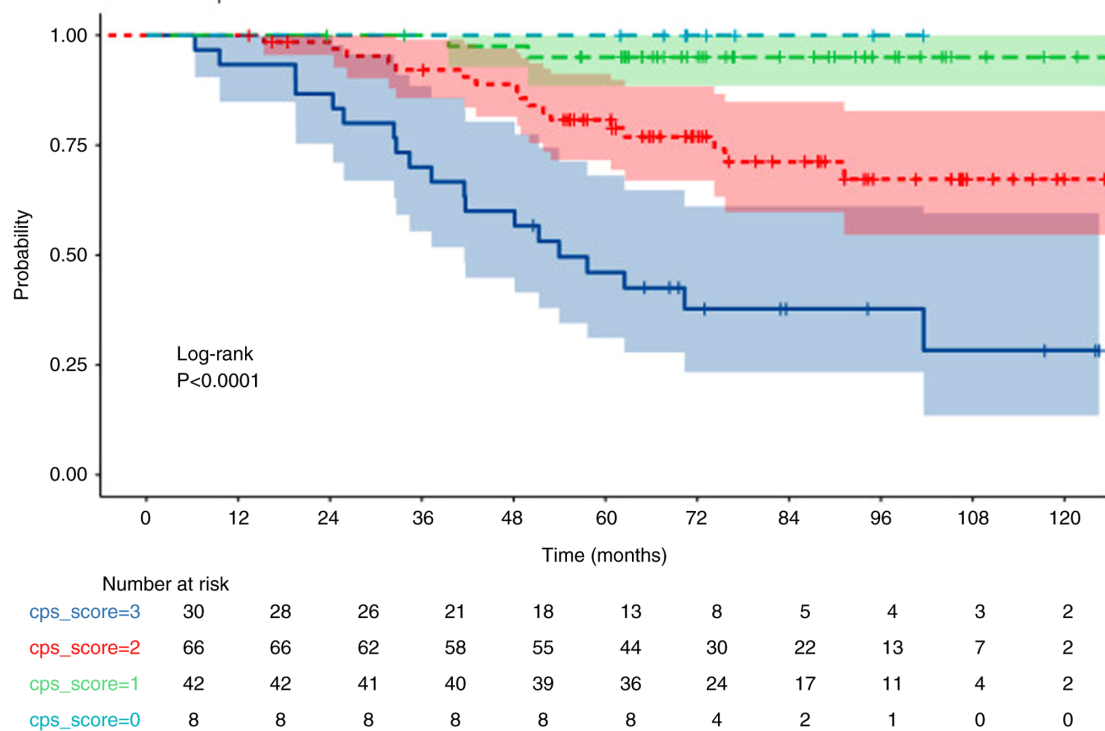


Figure 1. Overall survival of the study group according to CPS scores (0-1-2-3-4). CPS, clinical and pathological stage.

EG score (3-4-5) was predictive of a worse DFS (HR, 3.592; P=0.028), but its association with OS did not reach statistical significance (HR, 4.121; P=0.058). Age and tumor diameter

also did not demonstrate a significant impact on survival outcomes. These findings suggest that CPS and CPS + EG scores are valuable prognostic indicators, particularly for

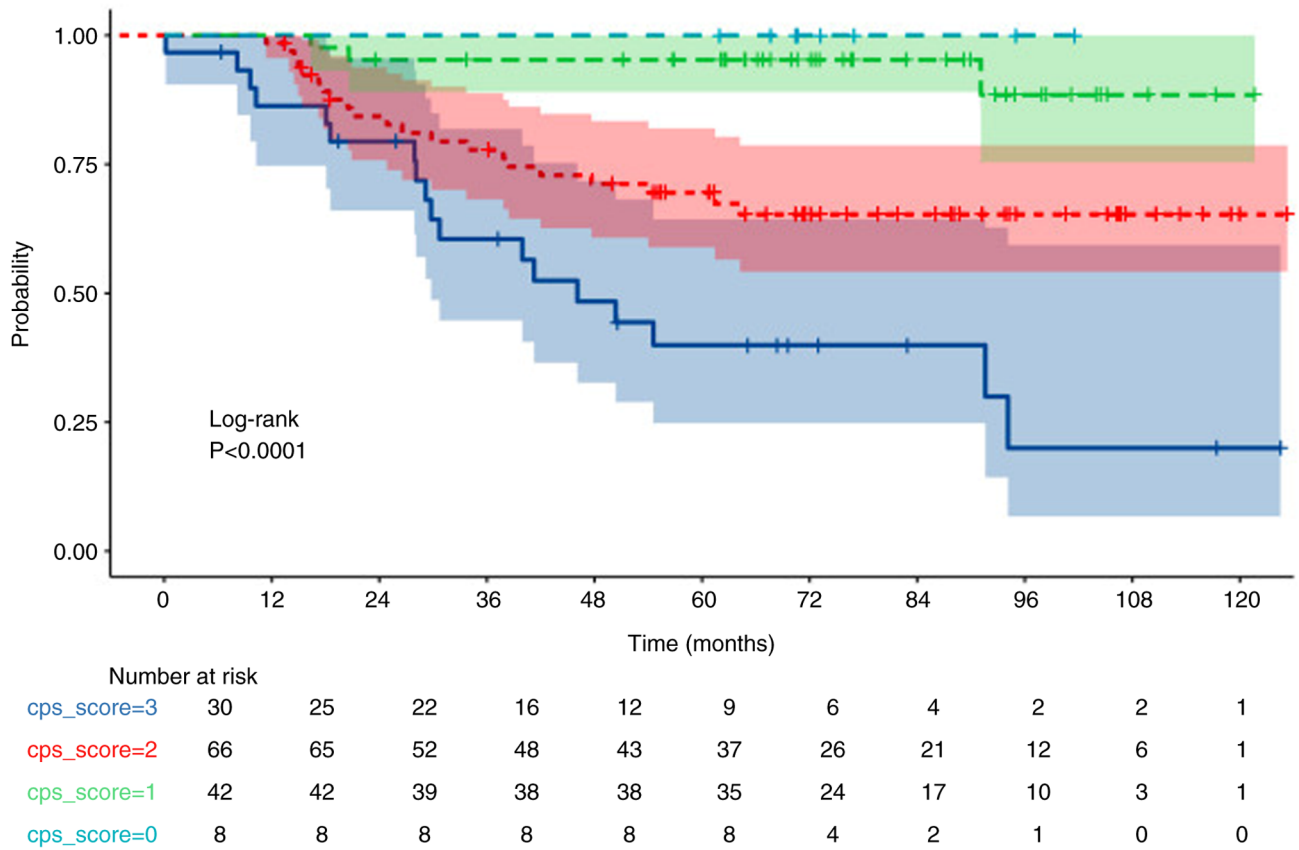


Figure 2. Disease-free survival of the study group according to CPS scores (0-1-2-3-4). CPS, clinical and pathological stage.

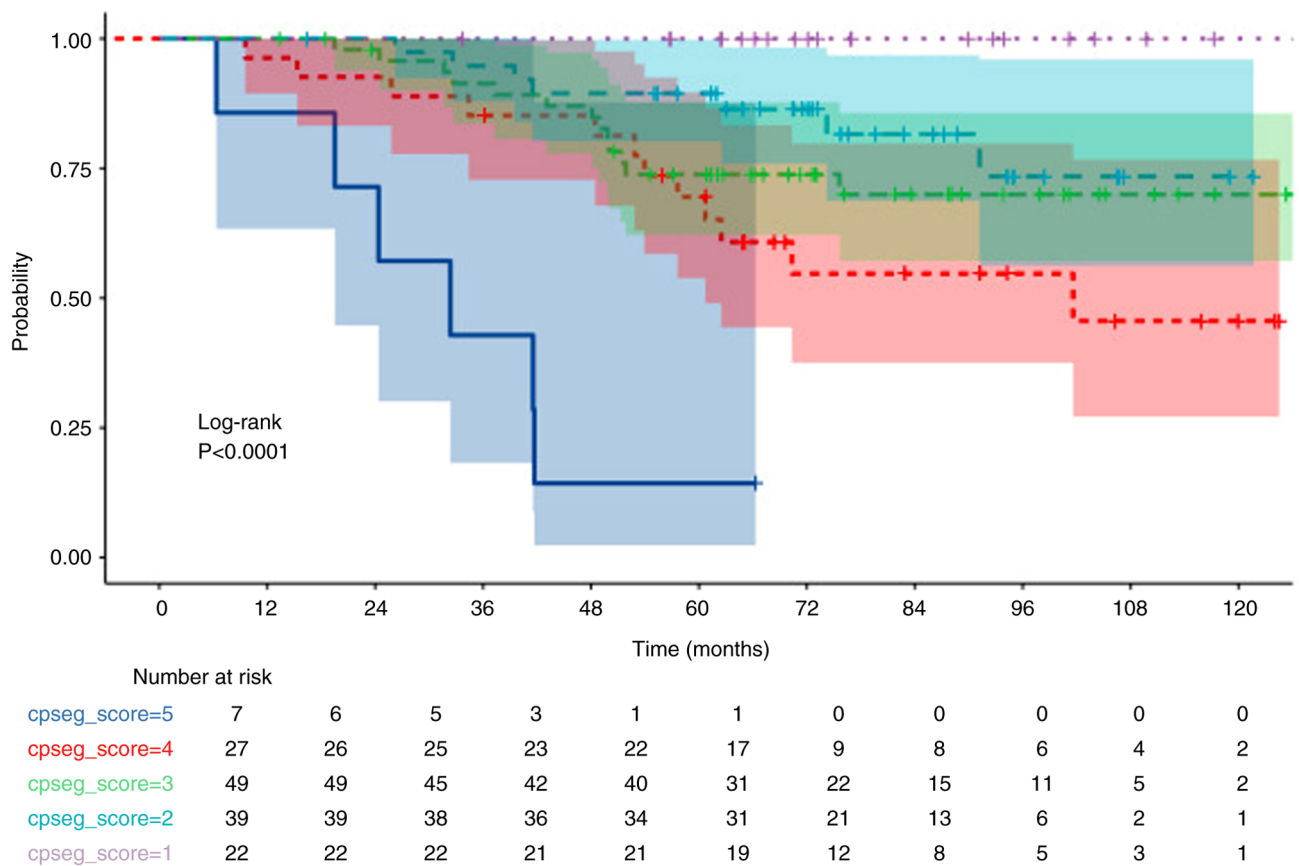


Figure 3. Overall survival of the study group according to CPS + EG scores (0-1-2-3-4-5). CPS, clinical and pathological stage; EG, estrogen receptor status and histologic grade.

Table V. Univariate analyses of several clinical parameters of patients in terms of overall survival and disease-free survival.

| A, Overall survival      |                       |         |
|--------------------------|-----------------------|---------|
| Variable                 | HR (95% CI)           | P-value |
| Age, years               | 1.010 (0.979-1.041)   | 0.542   |
| Tumor diameter, mm       | 1.014 (1.002-1.027)   | 0.027   |
| Relapse                  |                       | <0.001  |
| No                       | 1                     |         |
| Yes                      | 16.247 (7.124-37.258) |         |
| Menopause status         |                       | 0.122   |
| Pre-perimenopausal       | 1                     |         |
| Postmenopausal           | 1.670 (0.871-3.203)   |         |
| Clinical stage           |                       | 0.006   |
| 2A-2B                    | 1                     |         |
| 3A-3B-3C                 | 2.576 (1.316-5.043)   |         |
| HER2 status              |                       | 0.019   |
| Positive                 | 1                     |         |
| Negative                 | 2.447 (1.157-5.143)   |         |
| CPS score                |                       | <0.001  |
| 0-1-2                    | 1                     |         |
| 3-4                      | 5.111 (2.699-9.679)   |         |
| CPS + EG score           |                       | <0.001  |
| 0-1-2                    | 1                     |         |
| 3-4-5                    | 4.121 (1.813-9.367)   |         |
| B, Disease-free survival |                       |         |
| Variable                 | HR (95% CI)           | P-value |
| Age, years               | 0.996 (0.967-1.027)   | 0.809   |
| Tumor diameter, mm       | 1.012 (1.000-1.024)   | 0.046   |
| Relapse                  |                       | -       |
| No                       | -                     |         |
| Yes                      | -                     |         |
| Menopause status         |                       | 0.620   |
| Pre-perimenopausal       | 1                     |         |
| Postmenopausal           | 1.166 (0.636-2.137)   |         |
| Clinical stage           |                       | <0.001  |
| 2A-2B                    | 1                     |         |
| 3A-3B-3C                 | 2.696 (1.417-5.128)   |         |
| HER2 status              |                       | 0.024   |
| Positive                 | 1                     |         |
| Negative                 | 2.203 (1.107-4.384)   |         |
| CPS score                |                       | <0.001  |
| 0-1-2                    | 1                     |         |
| 3-4                      | 3.876 (2.095-7.173)   |         |
| CPS + EG score           |                       | <0.001  |
| 0-1-2                    | 1                     |         |
| 3-4-5                    | 3.592 (1.717-7.516)   |         |

HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; CPS, clinical and pathological stage; EG, estrogen receptor status and histologic grade.

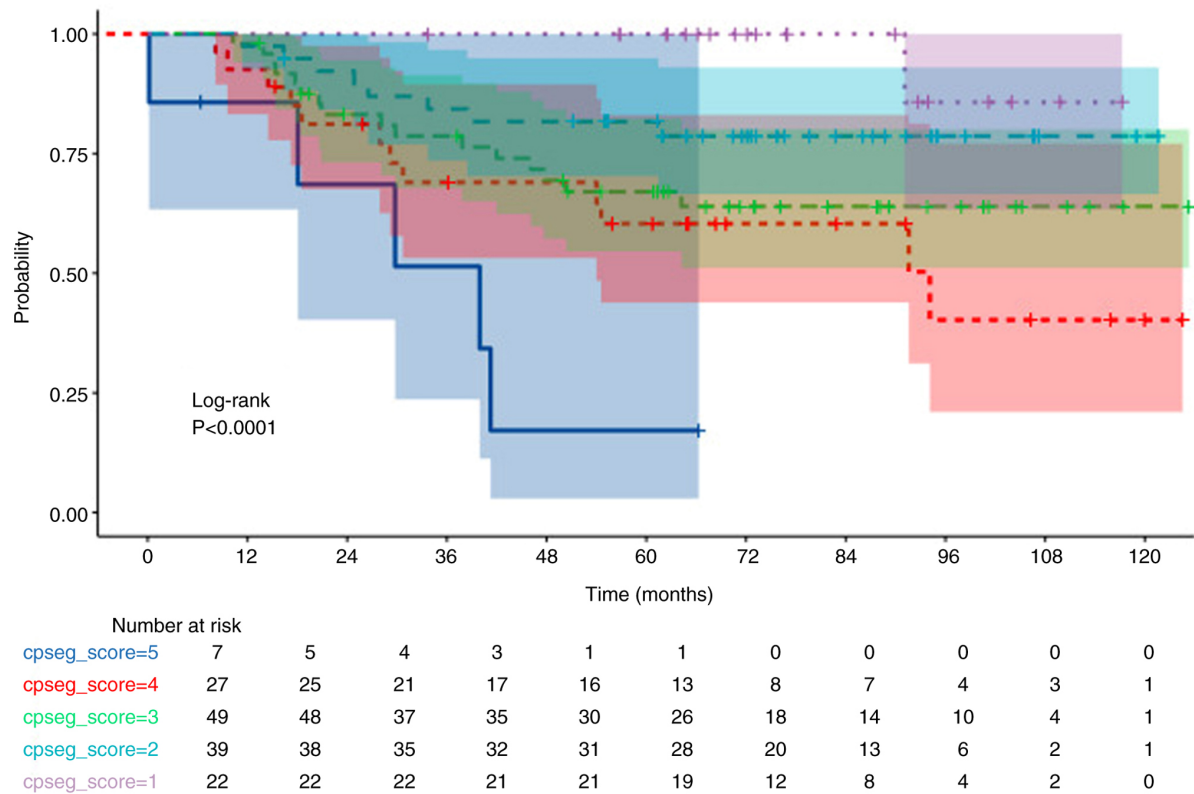


Figure 4. Disease-free survival of the research group according to CPS + EG scores (0-1-2-3-4-5). CPS, clinical and pathological stage; EG, estrogen receptor status and histologic grade.

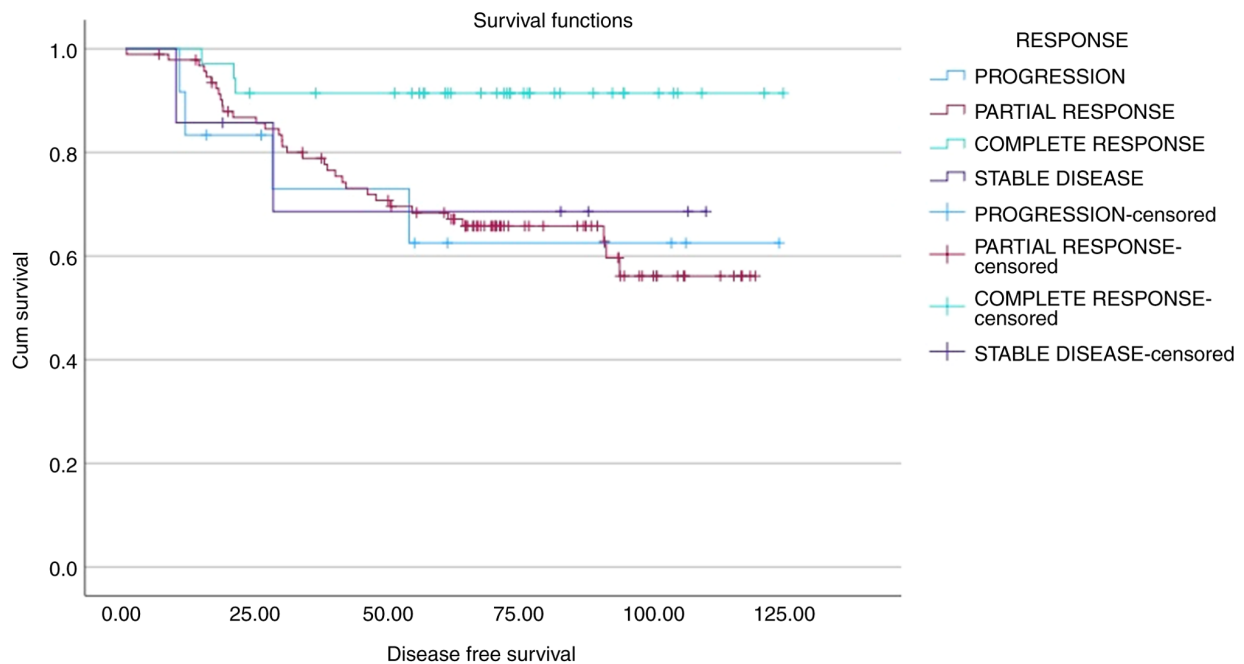


Figure 5. Disease free survival of the research group according to response rates as pCR and non pCR (progression, partial response, stable disease).

disease recurrence. Notably, the greatest increase in risk was observed in OS for higher CPS scores (HR, 5.111), indicating a more than five-fold increase in mortality risk, whilst HER2-negative status was associated with a two-fold increase in both mortality and recurrence (Table VI).

## Discussion

Determination of the prognosis in patients with breast cancer is important for several reasons: It has an important role in establishing the treatment decision and frequency of



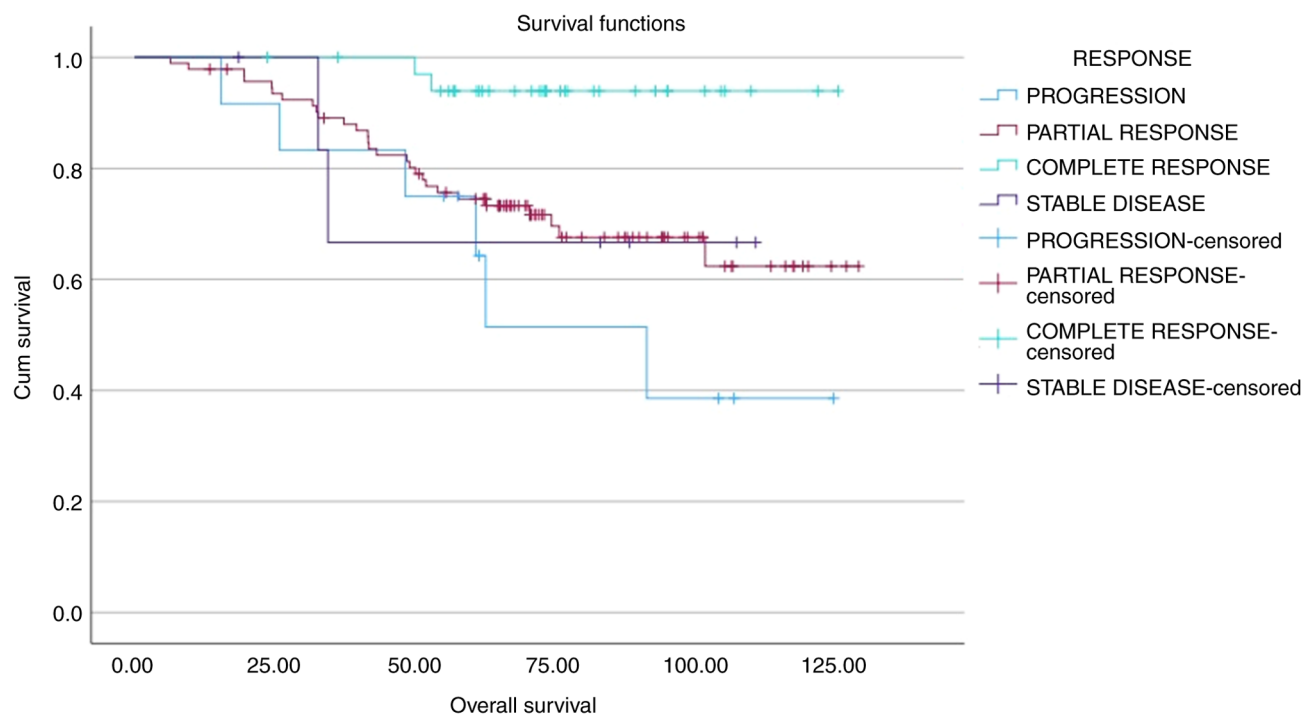


Figure 6. Overall survival of the research group according to response rates as pCR and non pCR (progression, partial response, stable disease).

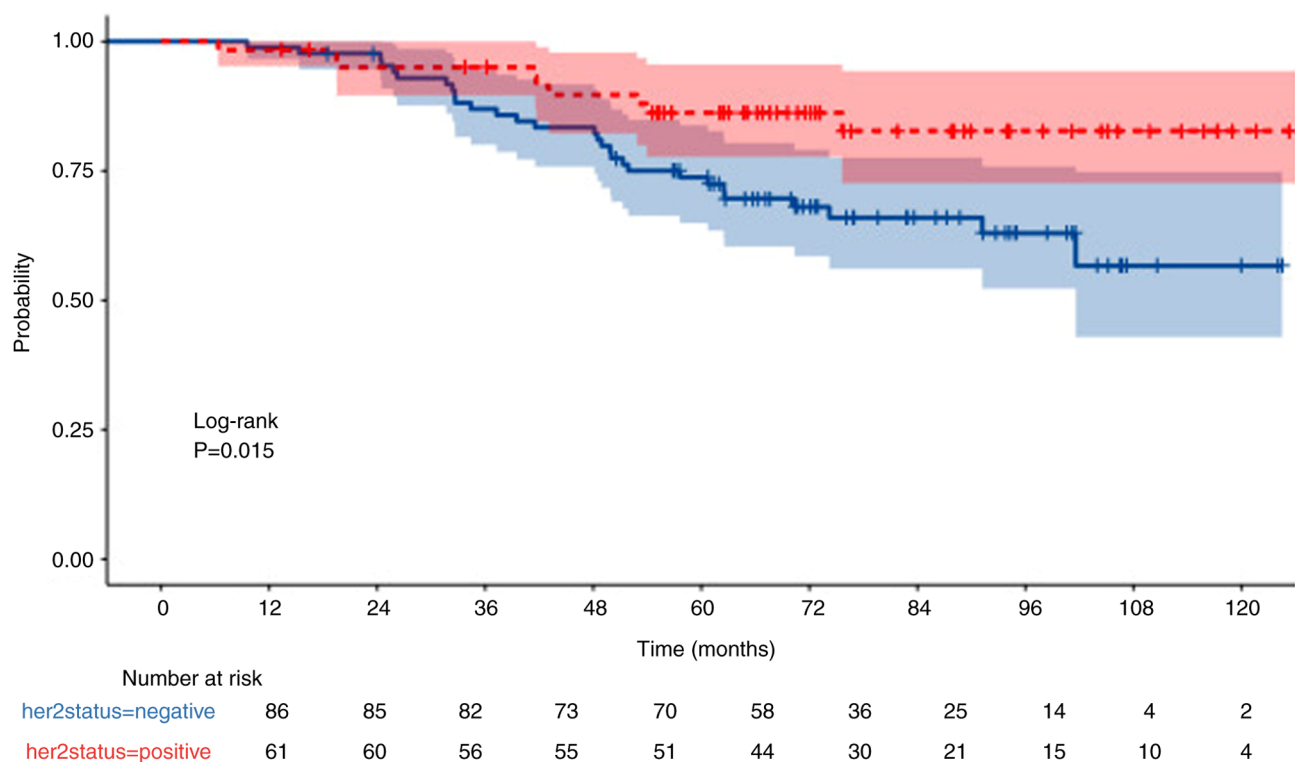


Figure 7. Overall survival of the research group according to the HER2 positivity and negativity status. HER2, human epidermal growth factor receptor 2.

follow-ups. Moreover, sharing the prognosis with patients and their relatives is an important reinforcement regarding quality of life. Relieving anxiety reduces depression and anxiety disorders along with increasing treatment compliance (11). Inclusion and stratification in clinical trials are also based on prognosis determination (12).

Prognostic acuity of the universally used TNM classification, established by the American Cancer Joint Committee has been defined. This system requires biopsy-based information, including ER, PR and HER2 status, and tumor grade and imaging for clinical staging (13). As an individualized approach is becoming more widespread in daily practice,



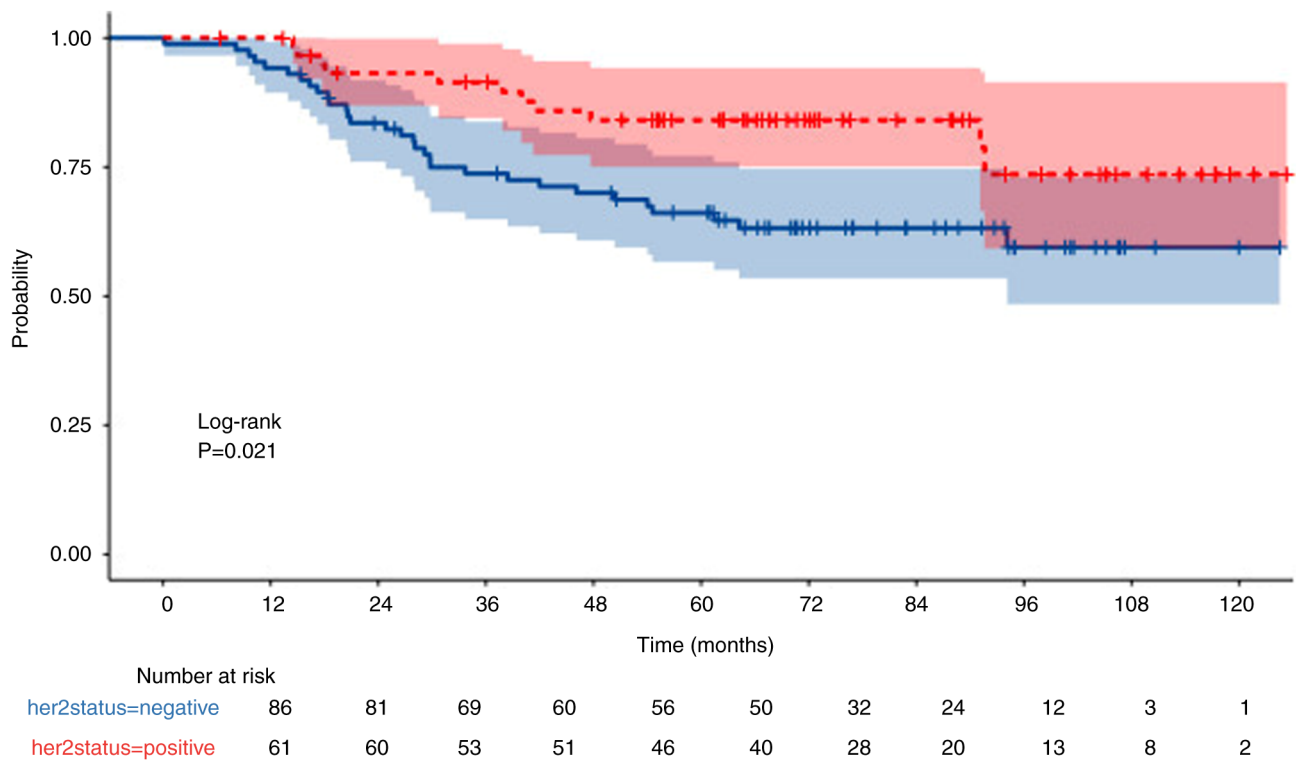


Figure 8. Disease-free survival of the research group according to the HER2 positivity and negativity status. HER2, human epidermal growth factor receptor 2.

prognostic models are needed to evaluate prognosis. According to the report published by the National Comprehensive Cancer Network, markers that carry descriptive, complementary and prognostic expressions of the disease should be able to express general terminology including analytical validity, clinical validity and clinical utility (14).

The utility and validity of the prognostic models are tested with validation studies (12). Prediction models should be validated using large cohorts from diverse ethnic groups to ensure that their impact on clinical decision-making does not interfere with the implementation of life-saving measures. Several prognostic models have been identified for predicting the outcomes of breast cancer; however, validation studies are insufficient. Their performances in independent populations are also suboptimal (15). Occasionally, internal validation works well but external validation may not (16). The Nottingham Prognostic Index is the oldest and easiest model in this field which was validated following different modifications (17-19).

Determining the validity of the CPS + EG scoring system will expand the use of this easily accessible and cost-effective system. It has been used in the stratification of other clinical trials for prognosis determination. Furthermore, it has been emphasized that this scoring system is valuable in the evaluation of local recurrence: The addition of postmastectomy radiotherapy to the treatment of a high-risk group with a CPS + EG score of  $>3$  was reported to be associated with reduced recurrence rates (20). The findings of the study by Marmé *et al* (21) of the CPS + EG scores following NACT in HR-positive and HER2-negative breast cancer groups were also consistent with the findings of the present study. However, the study assessed 5-year DFS and OS following NACT in

patients with triple negative breast cancer, and reported that the prognostic value of the scoring was 'insufficient'.

To assess prognosis, key factors such as patient age, tumor size, degree of invasion, receptor status and histological grade are typically evaluated. In the case of locally advanced hormone-positive breast cancer, genomic profiling tools, including Oncotype DX risk scoring, EndoPredict, PAM50, the Breast Cancer Index and MammaPrint Genomic profiling assist in distinguishing between in high-risk and low-risk tumors (22). However, the high costs associated with these tests have led many authorities to impose restrictions on their use. Moreover, the lack of insurance coverage of these tests presents a notable challenge, particularly for economically disadvantaged patients (23). In this context, the incorporation of cost-free and non-invasive prognostic alternatives could offer additional advantages in clinical decision-making.

Mortality rates of patients with HER2-positive breast cancer are lower than those of patients with HER2-negative breast cancer in both hormone-positive and -negative subgroups (24), and anti-HER2 treatments serve a marked role in these outcomes. A previous study reported that the hazard ratios of patients with HER2-positive breast cancer gradually decreased in the hormone-positive subgroup compared with the hormone-negative subgroup, whereas the hormone-negative subgroup hazard ratios did not change over time (25).

NACT has become an integral part of breast cancer management, particularly in recent decades. In addition to shrinking the tumor and reducing the extent of surgery, NACT serves a crucial role in tumor downstaging and holds prognostic significance. Whilst radiological imaging remains an important tool for assessing treatment response, pathological evaluation continues to be the gold standard (26). Treatment

Table VI. Multivariate analyses of several clinical parameters of patients in terms of overall survival and disease-free survival.

## A, Overall survival.

| Variable           | HR (95% CI)         | P-value |
|--------------------|---------------------|---------|
| Age, years         | 1.010 (0.979-1.041) | 0.826   |
| Tumor diameter, mm | 1.014 (1.002-1.027) | 0.348   |
| HER2 status        |                     | 0.038   |
| Positive           | 1                   |         |
| Negative           | 2.447 (1.157-5.143) |         |
| CPS score          |                     | 0.007   |
| 0-1-2              | 1                   |         |
| 3-4                | 5.111 (2.699-9.679) |         |
| CPS + EG score     |                     | 0.058   |
| 0-1-2              | 1                   |         |
| 3-4-5              | 4.121 (1.813-9.367) |         |

## B, Disease-free survival

| Variable           | HR (95% CI)         | P-value |
|--------------------|---------------------|---------|
| Age, years         | 0.996 (0.967-1.027) | 0.528   |
| Tumor diameter, mm | 1.012 (1.000-1.024) | 0.561   |
| HER2 status        |                     | 0.033   |
| Positive           | 1                   |         |
| Negative           | 2.203 (1.107-4.384) |         |
| CPS score          |                     | 0.025   |
| 0-1-2              | 1                   |         |
| 3-4                | 3.876 (2.095-7.173) |         |
| CPS + EG score     |                     | 0.028   |
| 0-1-2              | 1                   |         |
| 3-4-5              | 3.592 (1.717-7.516) |         |

HR, hazard ratio; CI, confidence interval; HER2, human epidermal growth factor receptor 2; CPS, clinical and pathological stage; EG, estrogen receptor status and histologic grade.

response and tumor histological subtype are key factors in predicting the effectiveness of NACT, particularly as achieving a pCR notably improves PFS and OS (27,28). However, whilst pCR is a well-established prognostic marker in HR-negative tumors, a German study reported that achieving pCR was not a surrogate marker for prognosis in patients with Luminal A and Luminal B/HER2 positive breast cancer (29,30). This finding underscores the notion that tumor biology is a more significant determinant of prognosis than the response to NACT.

There is currently insufficient evidence to support treatment modifications based solely on the CPS + EG score, to the best of our knowledge. In patients with low-risk breast cancer, radiotherapy omission has been recommended in selected cases (31). However, its association with the CPS + EG score has not been clearly established. Although the role of treatment escalation in patients with high CPS + EG scores is a matter of debate, no standardized approach has been established (20,32). Therefore, whilst the CPS + EG score is

a well-validated prognostic tool, its utility in guiding specific therapeutic decisions remains unclear.

The present study has certain limitations. First, age was not considered a distinguishing criterion. Given that breast cancer tends to exhibit a more aggressive course in younger (<35 years) and elderly (>65 years) patients, the predictive value of the CPS + EG scoring system may be less reliable in these age groups (33,34). Second, the present study did not incorporate genetic data, which may provide additional prognostic and predictive insights. Third, the relatively small sample size limits the generalizability of the findings. The small number of patients in subgroup analyses further reduced statistical power, making definitive conclusions more challenging. Additionally, heterogeneity in treatment regimens and clinical characteristics among patients may introduce variability in outcomes. Standardized treatment protocols in future prospective studies could help clarify the true impact of CPS + EG scoring in clinical decision-making. Finally, integrating CPS +

EG scoring with emerging molecular and imaging biomarkers could further improve risk stratification and facilitate personalized treatment strategies in breast cancer. Future research should explore these aspects to optimize patient outcomes.

In conclusion, although the clinical stage at the first presentation of the disease may provide information on the prognosis of the patient, incorporating biological markers to the equation refines the outcomes in patients treated with NACT. Prognostic models that are incorporated with biological markers with several parameters facilitate an individualized approach. In the present study, the CPS + EG scoring system effectively predicted the prognosis of patients with non-metastatic breast cancer treated with NACT. Estimating prognosis at the initial presentation may help to identify the escalation and intensification of the chemotherapy treatment needed during the neoadjuvant therapy period.

The present study is the first to assess the CPS + EG scoring system in real-life data from patients with hormone positive breast cancer in Turkey, to the best of our knowledge. Furthermore, it provides a valuable opportunity to provide comparisons with other data sets on mortality and OS rates. The findings of the present study demonstrate a clear association between the CPS + EG score and survival. As the score increases, both the probability of recovery and the OS decrease. The CPS + EG scoring system is an easy-to calculate, cost-effective and accessible tool for clinical follow-up, survival estimation and patient stratification in NACT trials along with adjuvant chemotherapy choices.

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#### Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

#### Authors' contributions

EYY collected and analyzed the data, and drafted the manuscript. SA planned the study and wrote the paper. OUU developed the study concept and reviewed the paper. EYY, SA and OUU confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

#### Ethics approval and consent to participate

Ethics approval for the present study was obtained from the local ethics committee of Izmir Tepecik Education and Research Hospital (approval no: 2023/08). As the present study was retrospective, informed patient consent was not required.

#### Patient consent for publication

Not applicable.

#### Competing interests

The authors declare that they have no competing interests.

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