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ORIGINAL RESEARCH

Patient-reported outcomes predict survival and adverse events following anticancer treatment initiation in advanced HER2-positive breast cancer

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Background: The prognostic value of patient-reported outcomes (PROs) has been minimally explored in advanced breast cancer (BC), and their comparative prognostic performance against Eastern Cooperative Oncology Group performance status (ECOG PS) is largely unknown.

Patients and methods: This study pooled individual participant data from clinical trials CLEOPATRA, EMILIA, and MARIANNE. Pre-treatment PRO associations with overall survival (OS), progression-free survival (PFS), and grade $\geq$3 adverse events were evaluated via Cox proportional hazards regression. Prognostic performance was assessed with the C-statistic (*c*). PRO values were collected via the Functional Assessment of Cancer Therapy—Breast (FACT-B) questionnaire. All analyses were stratified by study and treatment arms. Analyses adjusted for known prognostic variables were conducted. Exploratory analysis of the prognostic performance of PROs compared to ECOG PS was undertaken.

Results: The study included data from 2894 patients initiated on contemporary therapies including pertuzumab (n = 765), trastuzumab (n = 1173), trastuzumab emtansine (n = 1225), taxanes (n = 1173), lapatinib (n = 496), and capecitabine (n = 496). On univariable and adjusted analysis, patient-reported physical well-being, functional well-being, and BC subscale were all identified to be associated with OS, PFS, and grade $\geq$3 adverse events ($P < 0.05$). Patient-reported physical well-being was the most prognostic PRO for all assessed outcomes. The OS prognostic performance of physical well-being ($c = 0.58$) was superior to ECOG PS ($c = 0.56$) ($P < 0.05$), with multivariable analysis indicating that both provide independent information ($P < 0.0001$).

Conclusions: PROs were identified as independent prognostic factors for OS, PFS, and grade $\geq$3 adverse events in patients with human epidermal growth factor receptor 2 (HER2)-positive advanced BC initiating contemporary treatment options. Further, patient-reported physical well-being was more prognostic of OS than ECOG PS and contained independent information. PROs have value as prognostic and stratification factors for clinical use and research trials of anticancer treatment in HER2-positive ABC.

Key words: patient-reported outcomes, Eastern Cooperative Oncology Group performance status, advanced breast cancer, contemporary therapy, survival outcomes, toxicity outcomes

INTRODUCTION

Human epidermal growth factor receptor 2 (HER2)-positive breast cancer (BC) is an aggressive subtype of BC.[1] Evidence outlines that the emergence of targeted therapies such as trastuzumab, pertuzumab, and ado-trastuzumab emtansine (T-DM1) has improved survival outcomes in HER2-positive advanced BC (ABC).[2-5] Despite this, a persistent burden of unpredictable poor response remains for many patients, while others may experience significant toxicities.[2,6,7] Thus, predicting patients who are likely to achieve better or worse outcomes to contemporary anticancer treatment in HER2-positive ABC remains of significant interest to support shared decision making and precision medicine.

Shared decision making is the process in which the clinician and the patient collate and discuss the available evidence on the benefits and harms of treatments to make the most appropriate informed health decisions for the patient.[8] Shared decision making is an essential component of providing patient-centered care.[9] Eastern Cooperative Oncology Group performance status (ECOG PS) is a

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clinician-interpreted tool used to evaluate the daily living abilities of patients.[9] ECOG PS is often used for oncology trial stratification and in clinical practice to evaluate prognosis and toxicity to anticancer treatment, thus supporting shared decision making. Patient-reported outcomes (PROs) are structured self-reported tools that provide the patients' perspective and voice to their physical, social, emotional, and functional abilities.[10-12] PROs are frequently used in oncology trials as measures to evaluate treatment impacts on quality of life.[13-15] However, PRO tools are minimally used for oncology trial stratification, or in clinical practice to estimate likely benefits and harms from anticancer treatment.

PROs have shown to be of prognostic importance in other cancer types (including bladder cancer, non-small-cell lung cancer, and melanoma),[16-23] with some studies demonstrating patient-reported physical function/well-being as more prognostic than ECOG PS.[17,20,21,23] Additionally, PROs have shown the potential to detect serious adverse events earlier than clinician reporting.[24] However, the prognostic value of PROs in HER2-positive ABC has been minimally explored.

The present study aimed to evaluate the prognostic performance of pre-treatment PROs for prognosis and toxicity in patients initiating contemporary anticancer treatment of HER2-positive ABC.

MATERIAL AND METHODS

Patient population

Individual participant data (IPD) from the Roche-sponsored phase III clinical trials CLEOPATRA (NCT00567190, data cut: February 2014),[4,25,26] EMILIA (NCT00829166, data cut: December 2014),[5,27] and MARIANNE (NCT01120184, data cut: May 2016)[28,29] were utilized in this *post hoc* study. Data were accessed according to Roche policy and have been made available through Vivli, Inc. (www.vivli.org). Secondary analysis of anonymized IPD was exempted from review by the Southern Adelaide Local Health Network, Office for Research and Ethics as it was classified as minimal risk research.

CLEOPATRA included patients with HER2-positive, locally recurrent, unresectable, or metastatic BC that were treatment naive (excluding prior hormonal therapy) in the advanced setting. Patients were randomly assigned 1 : 1 to receive either placebo + trastuzumab + docetaxel, or pertuzumab + trastuzumab + docetaxel.[4,25,26]

EMILIA included heavily pre-treated patients with HER2-positive, unresectable, locally advanced, or metastatic BC with documented disease progression to trastuzumab and a taxane. Patients were randomly assigned 1 : 1 to either lapatinib + capecitabine or T-DM1.[5,27]

MARIANNE included patients with HER2-positive, unresectable, progressive, or recurrent locally advanced, or metastatic BC that were treatment naive in the advanced setting. Patients were randomly assigned 1 : 1 : 1 to trastuzumab + a taxane, T-DM1 + placebo, or T-DM1 + pertuzumab.[28,29]

Predictors and outcomes

Pre-treatment PROs were recorded using the Functional Assessment of Cancer Therapy—Breast (FACT-B) version 4.0 questionnaire in all three studies.[30] FACT-B is a self-reported 37-item questionnaire that measures multidimensional health-related quality of life in patients with BC. Responses to each question are captured on a five-point scale ranging from 0, 'Not at all' to 4, 'Very much'. Answers to the 37 questions are then used to calculate subscale scores. FACT-B has five subscales: physical well-being [score range (0-28)], social well-being (0-28), functional well-being (0-28), emotional well-being (0-24), and the BC subscale (0-40). Trial outcome index score (0-96) is a composite index of physical well-being, functional well-being, and the BC subscale. The five defined subscales are also used to generate a total FACT-B score (0-148). For all subscale scores, higher scores represent the patient's perception of 'better' health-related quality of life. The primary evaluated predictors in this study were pre-treatment physical well-being, social well-being, functional well-being, emotional well-being, and the BC subscale scores.

The primary assessed outcome was overall survival (OS), with progression-free survival (PFS) and grade $\geq$3 adverse events assessed as secondary outcomes. OS was defined as the time from randomization to the last follow-up or death from any cause—consistent across all studies. PFS was defined as the time from randomization to disease progression or death from any cause, with progression assessed using the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.0 (CLEOPATRA and EMILIA) or RECIST version 1.1 (MARIANNE).[5,26,28] Adverse events were reported in CLEOPATRA and EMILIA using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 3.0, and MARIANNE used NCI CTCAE version 4.0.[5,26,28]

Statistical analysis

Cox proportional hazard analysis was used to assess the association between pre-treatment PROs with OS, PFS, and grade $\geq$3 adverse events. All analyses were stratified by study and treatment arm. Associations were reported as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Statistical significance was set at a threshold of $P < 0.05$ and was determined via the likelihood ratio test. Complete case analyses were conducted. Discrimination performance was assessed using the concordance statistic (*c*-statistic). Akaike information criterion and visual checks were used to assess potential non-linear effects of continuous variables and cut-point appropriateness.

Univariable and analyses adjusted for race, sex, age, ECOG PS, body mass index, estrogen/progesterone receptor status, time since the initial diagnosis, presence of visceral disease, count of tumor disease sites, prior trastuzumab/anthracycline/taxane all settings, lactate dehydrogenase concentration, and comorbidity count were conducted.

Kaplan—Meier analysis was used to visually present the associations between PROs and survival/toxicity outcomes. For plotting, PROs were classified as 'Poor', 'Intermediate',

and 'Good' based on the interquartile range of each subscale in the study population. Forest plots were used to visualize the heterogeneity in the association between PROs and survival/toxicity outcomes according to study and treatment arms.

Exploratory analysis of the prognostic performance of PROs compared to ECOG PS was conducted and assessed via the *c*-statistic. All analyses were carried out using R version 3.6.2.

RESULTS

Patient population

Data were available from 2894 patients (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100475) treated with contemporary therapies from CLEOPATRA, EMILIA, and MARIANNE. Of the 2894 patients, 402 were randomized to receive pertuzumab + trastuzumab + docetaxel (HTP), 406 to placebo + trastuzumab + docetaxel (HT), 496 to lapatinib + capecitabine (LAPCAP), 495 to T-DM1 (T-DM1), 367 to placebo + T-DM1 (T-DM1), 365 to trastuzumab + docetaxel/paclitaxel (HT), and 363 to pertuzumab + T-DM1 (T-DM1+P) (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100475). Of the 2894 patients, 46 did not have available adverse event follow-up (Supplementary Table S1, available at https://doi.org/10.1016/j.esmoop.2022.100475). Supplementary Table S2, available at https://doi.org/10.1016/j.esmoop.2022.100475, presents the distribution of PROs within the pooled cohort according to study (missing data <10%). In the pooled cohort, 1535 patients experienced grade ≥3 adverse events. Median follow-up was 50 months (95% CI 49-51 months) in CLEOPATRA, 47 months (95% CI 45-48 months) in EMILIA, and 54 months (95% CI 54-55 months) in MARIANNE.

Prognostic associations of PROs with survival outcomes

In the pooled cohort, the association between pretreatment PROs and survival outcomes was best described by a linear association. The univariable and adjusted analysis identified significant associations for patient-reported physical well-being, trial outcome index score, total FACT-B score, functional well-being, and BC subscale score with OS (Table 1). Similar findings were also seen with PFS (Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100475). Of the identified significant PROs, patient-reported physical well-being was the most prognostic PRO for OS ($c = 0.60$) and PFS ($c = 0.55$) (Table 1 and Supplementary Table S3, available at https://doi.org/10.1016/j.esmoop.2022.100475).

Figure 1 presents the Kaplan–Meier estimates of survival outcomes by patient-reported physical well-being stratified by line of therapy. Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100475, present the forest plots of the association between physical well-being and survival outcomes by clinical trial arms. Figure 1, and Supplementary Figures S1 and S2, available at https://doi.org/10.1016/j.esmoop.2022.100475, demonstrate that patients self-reporting 'good' physical well-being had consistently improved survival outcomes compared to their counterparts who reported 'poor' physical well-being, irrespective of treatment or line of therapy.

Prognostic associations of PROs with grade ≥ 3 adverse events

Univariable and adjusted analysis identified significant associations for patient-reported physical well-being, trial outcome index score, total FACT-B score, functional well-being, and BC subscale score with grade ≥3 adverse events (Supplementary Table S4, available at https://doi.org/10.1016/j.esmoop.2022.100475). Patient-reported physical well-being ($c = 0.54$) was the most prognostic.

Figure 2 presents a Kaplan–Meier plot for the probability of developing grade ≥3 adverse events according to patient-reported physical well-being. Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100475, presents a forest plot of the association between physical well-being and grade ≥3 adverse events by clinical trial arms. Figure 2 and Supplementary Figure S3, available at https://doi.org/10.1016/j.esmoop.2022.100475, demonstrate patients self-reporting 'good' physical well-being consistently had less grade ≥3 adverse events compared to their counterparts who reported 'poor'

Table 1. Univariable and adjusted association between patient-reported outcomes and overall survival

Patient-reported outcomes	Univariable					Adjusted[a]			
	n	HR[b]	95% CI	*P* value	*c*	n	HR[b]	95% CI	*P* value
Physical well-being	2724	0.60	0.54-0.65	<0.001	0.60	2486	0.72	0.65-0.80	<0.001
Trial outcome index score	2680	0.83	0.80-0.86	<0.001	0.59	2449	0.87	0.84-0.91	<0.001
Total FACT-B score	2675	0.90	0.87-0.92	<0.001	0.57	2445	0.92	0.90-0.95	<0.001
Functional well-being	2749	0.75	0.69-0.82	<0.001	0.56	2503	0.83	0.76-0.92	<0.001
Breast cancer subscale	2697	0.76	0.70-0.83	<0.001	0.55	2465	0.77	0.70-0.85	<0.001
Emotional well-being	2700	0.86	0.78-0.96	0.008	0.52	2465	0.91	0.81-1.03	0.130
Social/family well-being	2718	0.96	0.88-1.05	0.383	0.51	2481	0.93	0.84-1.02	0.136

BMI, body mass index; *c*, concordance statistic; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; ER/PR, estrogen receptor/progesterone receptor; FACT-B, Functional Assessment of Cancer Therapy—Breast; HR, hazard ratio.

[a]Adjustment variables: sex, age, Asian race, ECOG PS, BMI, ER status, PR status, time since initial diagnosis, presence of visceral disease at baseline, count of tumor disease sites, any prior trastuzumab/anthracycline/taxane all settings, lactate dehydrogenase at baseline, and comorbidity count.

[b]HR based on a 10-unit increase.

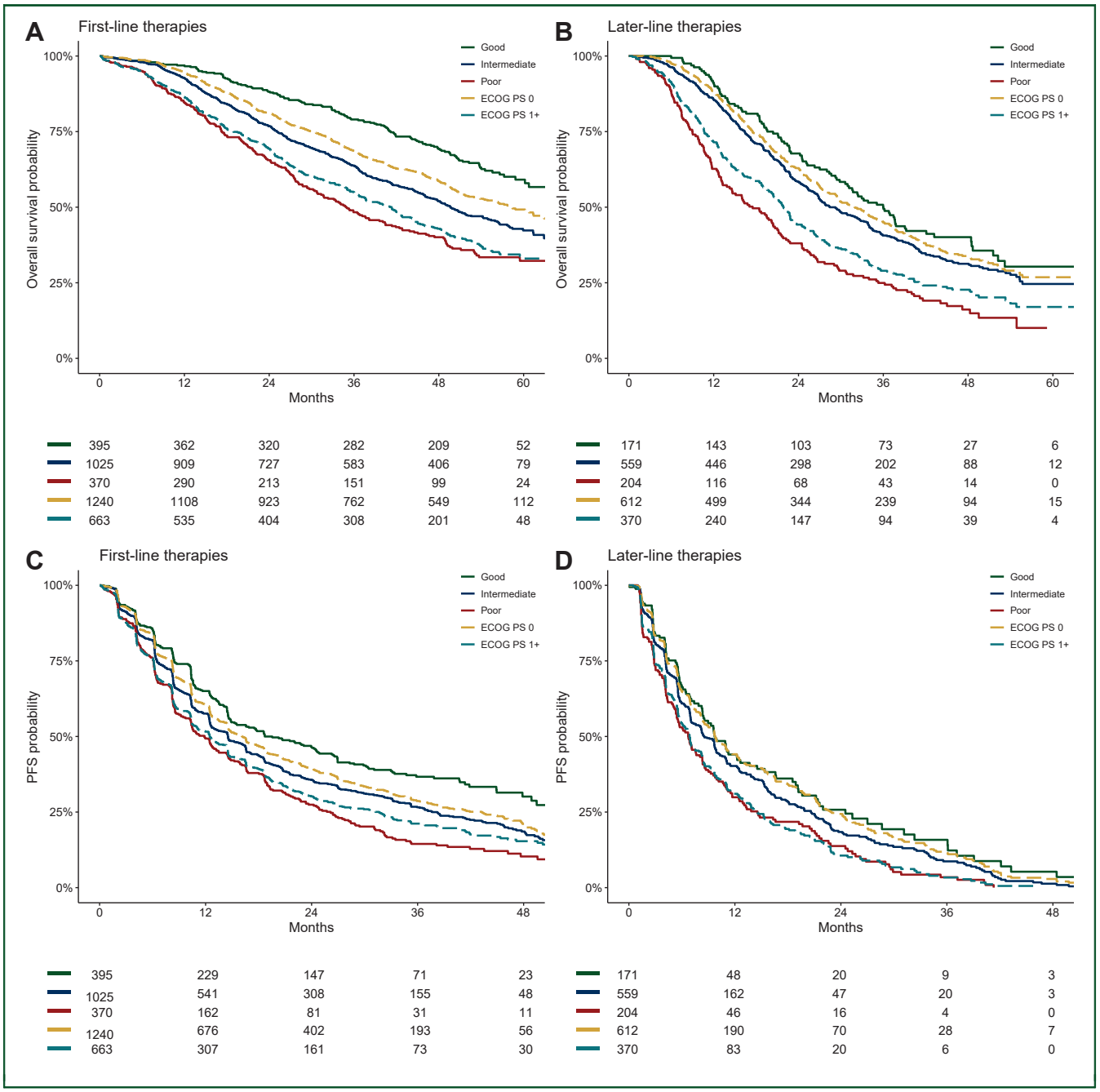

Figure 1. Kaplan–Meier estimates of survival outcomes by patient-reported physical well-being and ECOG PS for participants initiating first- and later-line therapies.

ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival.

physical well-being, irrespective of treatment or line of therapy.

Comparison of patient-reported physical well-being against ECOG PS

Of the 1852 patients who had an ECOG PS score of 0 (fully active, able to carry on all pre-disease performance without restriction), 215 (12%) and 1071 (58%) patients reported their physical well-being as 'poor' or 'intermediate', respectively (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100475). Further, of the 1852 patients with an ECOG PS of 0, >25% specifically reported that they lacked energy and were in pain (Supplementary Table S5, available at https://doi.org/10.1016/j.esmoop.2022.100475).

On exploratory analysis, the OS prognostic performance (*c*) of patient-reported physical well-being (low versus intermediate versus high) in the pooled cohort was 0.58. Comparably, the OS prognostic performance of clinician-interpreted ECOG PS was 0.56—this was statistically poorer than the patient-reported physical well-being groups

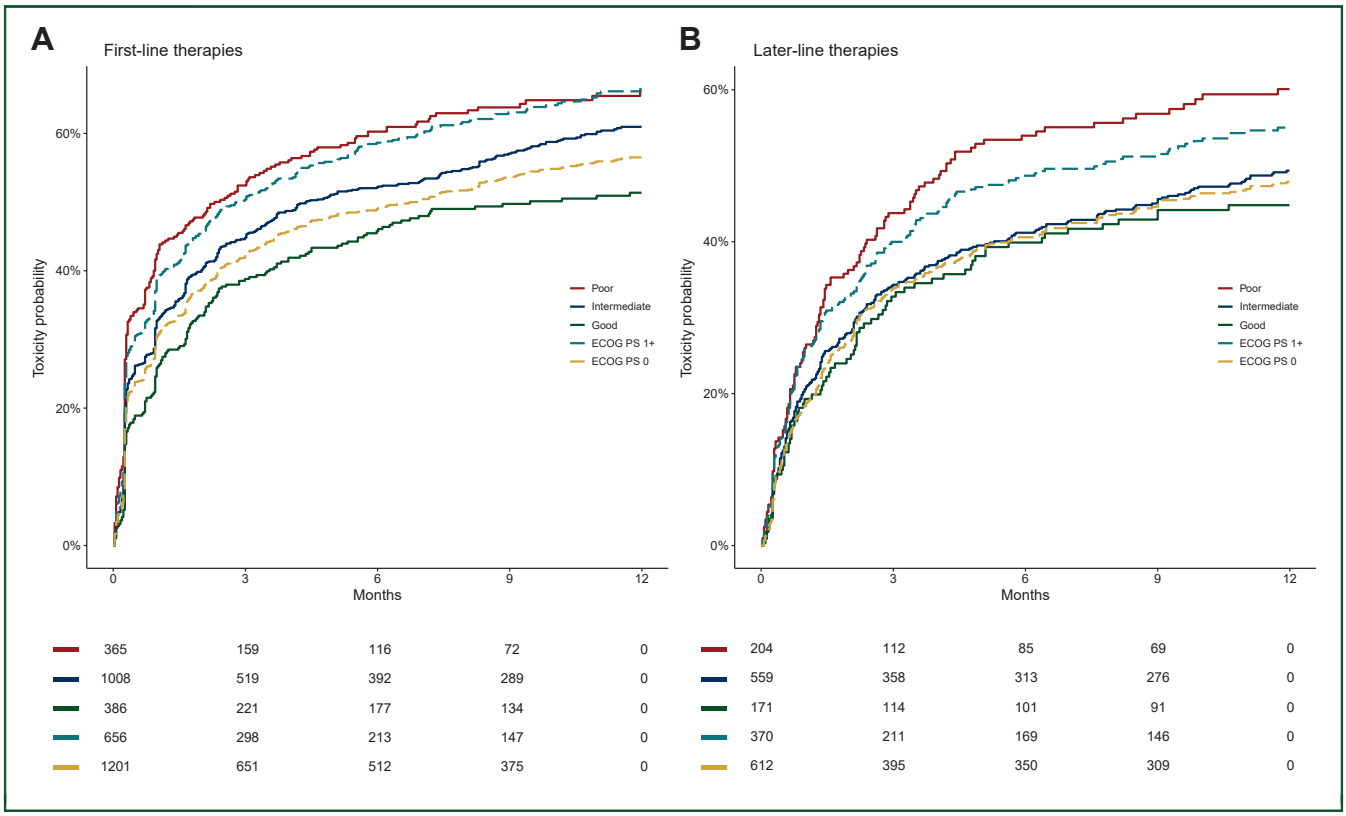

Figure 2. Kaplan–Meier estimates of grade ≥3 adverse events by patient-reported physical well-being and ECOG PS for participants initiating first- and later-line therapies.
ECOG PS, Eastern Cooperative Oncology Group performance status.

($P < 0.05$) (Table 2). Nonetheless, on multivariable analysis, both physical well-being and ECOG PS remained statistically significant, indicating that both provide independent prognostic information (Table 2). Similar findings were also observed for PFS and grade ≥3 adverse events (Table 2). Additionally demonstrating the higher discrimination performance of patient-reported physical well-being compared to ECOG PS, the OS probability at 36 months in the 'good' versus 'poor' physical well-being groups ranged from 79% to 48%. Opposingly, the OS probability at 36 months for ECOG PS of 0 versus 1+ ranged from 69% to 55% (Figure 1).

DISCUSSION

This study demonstrates for the first time that pretreatment PROs are significantly associated with OS, PFS, and grade ≥3 adverse events in patients with HER2-positive ABC treated with contemporary therapy. Additionally, this study found both patient-reported that physical well-being and clinician-interpreted ECOG PS provide independent prognostic information.

Patient-reported physical well-being, trial outcome index score, total FACT-B score, functional well-being, and BC subscale score were identified as significantly and independently associated with OS. Patient-reported physical well-being was the most prognostic PRO for primary and secondary outcomes. This is the first study to pool patients with HER2-positive ABC from three different trials that have been treated with contemporary therapies, and the results are consistent with recent findings in other advanced cancers.[16-21]

The American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO) have highlighted the identification of strategies that predict response and toxicity to anticancer therapies as key research priorities.[31,32] In this study, we utilized PROs to identify patients with HER2-positive ABC who are more likely to achieve better survival outcomes and patients who are more likely to experience grade ≥3 adverse events. Routine and longitudinal collection of PROs in patients with advanced solid tumors treated with chemotherapy has been shown to improve quality of life, satisfaction, and survival outcomes.[33-35] PreCycle (NCT03220178), a multicenter, randomized phase IV trial assessing the impact of longitudinally collected electronic PROs, is showing positive preliminary results in patients with HR-positive/HER2-negative ABC.[36] Our study shows the potential value of PRO tools for facilitating shared decision making and prognostic analysis in patients with HER2-positive ABC treated with a diverse range of anti-HER2 therapies. Therefore, we implore that the findings from this study are used to design strategies that bridge the gap between trials and routine clinical trials—as PROs are quite clearly prognostic of survival and toxicity for all the major contemporary treatment options in this ABC subtype.

At present, PROs are primarily used in the oncology setting—as secondary outcomes of clinical trials to

Table 2. Associations between patient-reported physical well-being and ECOG PS with overall survival, progression-free survival, and grade ≥3 adverse events

Predictors	Univariable					Multivariable[a]			
	n	HR[b]	95% CI	*P* value	*c*	n	HR[b]	95% CI	*P* value
Overall survival									
Physical well-being				<0.001	0.58				<0.001
Good[c]	566	1				563	1		
Intermediate[d]	1584	1.50	1.30-1.74			1583	1.45	1.25-1.68	
Poor[e]	574	2.40	2.03-2.84			572	2.10	1.76-2.49	
ECOG PS				<0.001	0.56				<0.001
0	1852	1				1740	1		
1+	1033	1.59	1.44-1.76			978	1.39	1.24-1.55	
Progression-free survival									
Physical well-being				<0.001	0.55				<0.001
Good[c]	566	1				563	1		
Intermediate[d]	1584	1.30	1.15-1.47			1583	1.27	1.12-1.43	
Poor[e]	574	1.73	1.50-2.00			572	1.59	1.37-1.84	
ECOG PS				<0.001	0.54				<0.001
0	1852	1				1740	1		
1+	1033	1.34	1.22-1.47			978	1.23	1.11-1.35	
Grade ≥3 adverse events									
Physical well-being				<0.001	0.53				0.004
Good[c]	557	1				554	1		
Intermediate[d]	1567	1.17	1.02-1.35			1566	1.15	1.00-1.32	
Poor[e]	569	1.42	1.21-1.67			567	1.33	1.12-1.57	
ECOG PS				<0.001	0.53				<0.001
0	1813	1				1713	1		
1+	1026	1.30	1.17-1.44			974	1.22	1.09-1.36	

c, concordance statistic; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio.
[a]Model includes both pre-treatment physical well-being groups and ECOG PS.
[b]HR based on a 10-unit increase.
[c]Good physical well-being ≥2.6.
[d]Intermediate physical well-being 1.8-2.59.
[e]Poor physical well-being <1.8.

strengthen the interpretation of the primary outcomes (efficacy, safety, etc.).[13-15] ESMO advocates the use of PROs as a co-primary endpoint in oncology trials, while the Food and Drug Administration is additionally advocating for their routine and standardized use as trial outcomes.[37,38] Outside this, PROs are not used in oncology trial stratification and their clinical utility is only now emerging. Opposingly, clinician-interpreted ECOG PS is routinely used to assess the eligibility of patients for clinical trials, as a prognostic factor for survival and toxicity outcomes in advanced cancers, and as an outcome measure.[39,40] The present study demonstrates that patient-reported physical well-being has independent, and potentially superior, prognostic performance to the clinician-interpreted ECOG PS. It is, therefore, essential that clinical practice transforms to place a greater emphasis on the patient's perspective and voice.

The findings of the present study are consistent with prior findings of patient-reported physical function/physical well-being and ECOG PS providing independent prognostic information.[17,20,21] It was interesting to note that 12% and 58% of patients classified as ECOG PS 0 reported poor and intermediate physical well-being, respectively. This indicates that 70% of the patients who were defined by their clinicians as 'fully active, and able to carry on all pre-disease performance without restrictions' reported limitations in their physical well-being status. The discordance between clinician-interpreted ECOG PS and patient-reported physical well-being suggests that appreciation of both parameters could allow for a more comprehensive prognostication of likely outcomes. Furthermore, it could be considered whether pre-treatment patient-reported physical well-being can be used as a stratification factor in clinical trials to optimize standardization between treatment arms.

Randomized controlled trials (RCTs) are the backbone of evidence-based medicine; however, strict inclusion criteria within RCTs can limit the generalizability of results (e.g. the study cohort was almost entirely restricted to participants with an ECOG PS of ≤1).[41] It is also acknowledged that some PRO data were missing—as some patients may not have answered the FACT-B questionnaire at baseline. However, RCTs provide a rigorous, high-quality collection of PROs, survival outcomes, and adverse event data.[42] Additionally, this study pooled large ($n = 2894$) data from three trials (CLEOPATRA, EMILIA, and MARIANNE) to increase study power and generalizability. Ultimately, this helped in assessing the relationship between clinician-interpreted ECOG PS and patient-reported physical well-being in patients with HER2-positive ABC. Effective communication is a core component of shared decision making[43] and can be enhanced with the use of patient-reported questionnaires that incorporate health-related quality of life measures as well as clinically interpreted measures. Future research should examine the association between ECOG PS and PROs in early BC, other BC subtypes, and in real-world populations—which are more likely to have broader distributions of ECOG PS and PROs scores.

In conclusion, pre-treatment PROs had a significant relationship with both survival and toxicity outcomes in patients with HER2-positive ABC, initiating contemporary anticancer treatment. Additionally, patient-reported physical well-being and clinician-interpreted ECOG PS were found to provide independent prognostic information. The study highlights the potential of combining patient-reported questionnaires and clinically interpreted measures to enhance clinical trial design and provide clinical insights that facilitate shared decision making in BC.

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DATA SHARING

This publication is based on data available from Roche according to its policy and process for individual participant data sharing at Vivli, Inc.

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