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Unfavorable Prognostic Impact of HER2 2+/FISH-Negativity in Older Patients with HER2-Negative and High-Risk Breast Cancer

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Purpose: Human epidermal growth factor receptor 2 (HER2)-low breast cancer, consisted of carcinomas with HER2 protein 1+ or 2+ without gene amplification, has been considered a biologically heterogeneous disease. Limited research separately investigated the prognostic significance of HER2 2+ without gene amplification, and no evidence can be identified in older patients. In this dedicated cohort of older patients with HER2-negative and high-risk breast cancer, we analyzed the real-world prognosis after standard adjuvant chemotherapy, and investigated the associations of survival with HER2 2+ without gene amplification.

Patients and Methods: From January 2016 to December 2021, older patients (≥65 years) with breast cancer were reviewed, and HER2-negative/high-risk disease receiving standard adjuvant chemotherapy was included. HER2-negativity was defined as immunohistochemistry (IHC) score 0, 1+ or 2+ without gene amplification by fluorescent in situ hybridization (FISH). Cox proportional hazards regression analyses were performed to assess the associations of HER2 2+/FISH-negativity with disease-free survival (DFS), which was estimated by the Kaplan–Meier method and compared by the Log rank test.

Results: This cohort consisted of 121 consecutive older patients. With a median follow-up of 46 months, 12 patients had a DFS event. By univariate and multivariate analyses, HER2 2+/FISH-negativity was the only independent predictor for worse DFS (hazard ratio 5.56; P=0.046). Patients with HER2 2+/FISH-negativity had significantly poorer DFS compared with those with HER2 0 or 1+ (Log rank test, P=0.029). In both hormone receptor (HR)-positive (Log rank test, P=0.052) and HR-negative (Log rank test, P=0.125) subgroups, HER2 2+/FISH-negativity showed a marginally significant adverse influence on DFS.

Conclusion: In older patients with HER2-negative/high-risk breast cancer undergoing standard adjuvant chemotherapy, our findings suggest that HER2 2+/FISH-negativity has an independent negative impact on prognosis.

Keywords: breast cancer, older patients, HER2-low, HER2 2+, prognosis

Introduction

Breast cancer is the most common cancer type and the leading cause of cancer death among females worldwide.[1] Ageing is a predominant risk factor for female breast cancer in terms of incidence and mortality.[2] The chronological age criterion for defining breast cancer in older patients is variably reported, commonly ≥65 or 70 years. In China in 2008, 16.6% of patients with breast cancer were aged 65 years or older, and by 2030, the proportion of this age group is estimated to be 27.0%.[3] A similar trend can be identified in group aged ≥70 years.[4,5] Management of older patients with breast cancer has become a routine part of clinical practice.

Older individuals are under-represented in clinical trials underpinning breast cancer treatment. Anticancer therapy is largely based on retrospective analyses and extrapolation of prospective evidence from their younger counterparts.[6–8] Furthermore, older population is highly heterogeneous, and treatment effect might be influenced by multiple factors, such

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as competing comorbidities, organ function decline, cognitive impairments, and patient preferences.[6–8] In real-world scenarios, management of breast cancer in older patients lacks guideline-concordant care with a substantial degree of variation in treatment strategies and clinical outcomes, implying potential undertreatment and relative poorer prognosis compared with their younger counterparts.[9–11] In the aspect of adjuvant chemotherapy, the complexity of older patients makes decision-making challenging and overcautious with a tendency to a more conservative approach. Nevertheless, high-risk disease can derive survival benefit from adjuvant chemotherapy, which should not be contraindicated in fit older individuals.[6–8] The US Oncology Research Trial 9735 and Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis consistently demonstrated that the survival benefit of adjuvant chemotherapy is of the similar magnitude in older and younger patients.[12,13] However, despite of extensive studies in younger patients, prognostic research for older population in real-world setting is lacking, and meaningful prognostic factors in older individuals with breast cancer after adjuvant chemotherapy remain unclear.

Human epidermal growth factor receptor 2 (HER2) has been widely recognized as an unfavorable prognostic factor in breast cancer. HER2 status is routinely assessed by immunohistochemistry (IHC) for protein expression and/or in situ hybridization (ISH) for gene amplification.[14] According to elevated degrees of HER2 immunostaining, HER2-negative disease has been categorized as IHC score 0, 1+ or 2+ without gene amplification by ISH (2+/ISH-negativity), and the latter two constitute the category of HER2-low breast cancer. Compared with HER2 0 tumors, no definite molecular and survival differences have been identified in HER2-low tumors, and HER2-low category has not been considered a distinct molecular entity, but rather a heterogeneous group of tumors with a wide spectrum of HER2 expression.[15,16] Among this heterogeneous disease, limited research has individually investigated the prognostic significance of HER2 2+/ISH-negativity. In younger patients, different levels of HER2 expression showed distinct biological characteristics and prognostic significance, and HER2 2+/ISH-negativity has a negative influence on survival outcomes in comparison with HER2 0 and/or 1+ status.[17–19] Nonetheless, to our knowledge, no prior research specially focused on the older population, and no evidence can be found about the correlation of HER2 2+/ISH-negativity with prognosis in older patients with HER2-negative breast cancer.

The aim of the current study was to investigate the prognostic impact of HER2 2+ without gene amplification in older patients with HER2-negative and high-risk breast cancer undergoing standard adjuvant chemotherapy.

Materials and Methods

Eligibility

Older patients with breast cancer diagnosed and treated in our center from January 2016 to December 2021 were reviewed. Patients were eligible if they met the following criteria: (1) female; (2) age 65 years or older[20] with a Charlson comorbidity index ≤2;[21] (3) confirmed HER2-negative invasive disease by IHC and/or fluorescent in situ hybridization (FISH); (4) no distant metastasis; (5) completion of upfront radical surgery; (6) high-risk tumor determined by one of the following risk factors on postoperative pathology: tumor size ≥2 cm, axillary lymph node metastasis, histological grade 3, negativity of estrogen receptor (ER), or Ki67 score ≥30%;[20,22–24] (7) completion of predetermined cycles of standard adjuvant chemotherapy containing taxanes and/or anthracyclines, and relative-dose intensity should be 85% or more; (8) available data of clinicopathological parameters and follow-up. This study was approved by the Ethics Committee of Sichuan Cancer Hospital (No. SCCHEC-02-2023-030) and was conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all individual participants included in the study.

Treatment

Breast conservation or mastectomy was performed based on individual characteristics of patients. Sentinel lymph node biopsy (SLNB) was conducted in patients with clinically node-negative axilla, and axillary lymph node dissection (ALND) can be omitted for those with no axillary metastasis or limited nodal involvement, which met the criteria of ACOSOG Z0011 trial.[25] For biopsy-proven node-positive disease, ALND was performed directly. All included patients were required to complete all prescribed cycles of standard adjuvant chemotherapy containing taxines and/or anthracyclines and relative-dose intensity lower than 85% was not allowed. Adjuvant radiotherapy was recommended for patients

with nodal metastasis or treated with breast-conserving surgery. Adjuvant endocrine therapy was recommended for patients with positive status of estrogen and/or progesterone receptor (PR).

Pathology

Pathological information of each included patient was reviewed based on postoperative pathology, respectively. HER2-negativity was defined as IHC score 0, 1+ or 2+ without gene amplification by FISH.[14] ER and PR were judged as positive if ≥1% of tumor cells had nuclear staining.[26] Hormone receptor (HR) was defined as positive if ER and/or PR was positive, while negativity for both ER and PR was considered as HR-negativity.[26] Histological grade was assigned according to the Scarff–Bloom–Richardson classification modified by Elston and Ellis.[27] The Ki67 score was determined as the percentage of nuclear stained cells among at least 1000 tumor cells counted.

Statistical Analysis

Statistical analyses were performed using SPSS 26.0 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 9 (GraphPad Software, San Diego, CA, USA). The endpoint of the current study was disease-free survival (DFS), which was defined as the interval between pathological diagnosis and local recurrence, distant metastasis, death from any cause, or termination of follow-up. Univariate and multivariate Cox proportional hazards regression analyses were conducted to investigate the correlation of DFS with clinicopathological characteristics. The Kaplan-Meier method was employed to draw DFS curves, and DFS was compared by the Log rank test. All *P* values were two-sided, and statistical significance was defined as $P < 0.05$.

Results

Patients

From January 2016 to December 2021, a total of 440 breast cancers in older patients were reviewed comprehensively, and 121 consecutive patients met the criteria for inclusion in this study. Patient characteristics of the entire population are summarized in Table 1. Median age was 67 years (range 65–75). Most tumors (62.8%) were pathological T2–3 stage, and 46 patients (38.0%) had pathological nodal metastasis. Histologically, 92.6% of tumors were invasive carcinoma of no special type, and 45 patients (37.2%) had tumors with grade 3. The Ki67 score ranged from 5% to 90%, and 68 tumors (56.2%) had Ki67 ≥30%. HR status was positive in 68.6% of patients. For HER2 expression, 62 tumors (51.2%) showed HER2 2+/FISH-negativity, compared with 59 tumors (48.8%) for IHC score 0 or 1+.

Table 1 Patient Characteristics

Characteristic	No. (*n*=121)	%
Age, years		
≤67	73	60.3
>67	48	39.7
Pathological T Stage[a]		
T1	45	37.2
T2–3	76	62.8
Pathological N Stage[a]		
N0	75	62.0
N1–3	46	38.0
Histology		
No special type	112	92.6
Others	9	7.4
Histological grade		
3	45	37.2
1–2	76	62.8

(*Continued*)

Table 1 (Continued).

Characteristic	No. (*n*=121)	%
Ki67 score		
≥30%	68	56.2
<30%	53	43.8
HR status		
Negative	38	31.4
Positive	83	68.6
HER2 status		
2+/FISH-negativity	62	51.2
0/1+	59	48.8
Surgery of the breast		
Mastectomy	76	62.8
Breast conservation	45	37.2
Surgery of the axilla		
SLNB	80	66.1
ALND	41	33.9
Adjuvant chemotherapy		
AC/TC	63	52.1
AC–T	58	47.9
Adjuvant endocrine therapy		
Yes	78	64.5
No	43	35.5
Adjuvant radiotherapy		
Yes	67	55.4
No	54	44.6
Survival event		
Yes	12	9.9
No	109	90.1

Notes: [a] T and N stage assessed using the 8th edition of American Joint Committee on Cancer TNM staging system.
Abbreviations: HR, hormone receptor; FISH, fluorescent in situ hybridization; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; AC, anthracycline plus cyclophosphamide; TC, taxane plus cyclophosphamide; AC–T, anthracycline plus cyclophosphamide followed by taxane.

Regarding surgery, most patients underwent mastectomy (62.8%) or SLNB (66.1%). For adjuvant chemotherapy, 58 patients (47.9%) received an anthracycline plus cyclophosphamide followed by a taxane (AC-T), 51 patients (42.1%) underwent a taxane plus cyclophosphamide (TC), and 12 patients (9.9%) were treated with an anthracycline plus cyclophosphamide (AC). Adjuvant treatment was performed in 78 patients (64.5%) for endocrine therapy, and in 55.4% of patients for radiotherapy, respectively. Over a median follow-up of 46 months (range 15–83), DFS events occurred in 12 patients, consisted of 3 local recurrences and 9 distant metastases.

Prognostic Impact of HER2 2+/FISH-Negativity

Univariate and multivariate Cox proportional hazards regression analyses were employed to investigate the prognostic impact of clinicopathological characteristics on DFS (Table 2). Univariate analysis suggested that HR-negativity (hazard ratio 3.69; 95% CI 1.17–11.63; *P*=0.026) and HER2 2+/FISH-negativity (hazard ratio 4.66; 95% CI 1.02–21.26; *P*=0.047) were significantly associated with poorer DFS. Adjuvant endocrine therapy (hazard ratio 0.24; 95% CI 0.07–0.78; *P*=0.018) showed a significant favorable influence on DFS. Age, pathological T stage, pathological N stage, tumor histology, histological grade, Ki67 score, adjuvant chemotherapy, and radiotherapy had no significant

Table 2 Associations of Clinicopathological Characteristics with DFS in Cox Proportional Hazard Regression Analyses

Characteristics	Univariate Analysis			Multivariate Analysis		
	Hazard Ratio	95% CI	*P* value	Hazard Ratio	95% CI	*P* value
Age, years (≤67 vs >67)	0.62	0.20–1.93	0.409	1.32	0.29–6.02	0.721
Pathological T stage (T1 vs T2–3)	0.83	0.25–2.76	0.762	0.99	0.25–3.95	0.992
Pathological N stage (N0 vs N1–3)	0.54	0.17–1.67	0.282	0.44	0.09–2.08	0.300
Histology (No special type vs others)	0.90	0.12–6.98	0.920	0.84	0.10–7.19	0.872
Histological grade (3 vs 1–2)	1.80	0.58–5.58	0.309	1.27	0.29–5.54	0.751
Ki67 score (≥30% vs <30%)	2.45	0.66–9.06	0.179	1.35	0.28–6.47	0.709
HR status (Negative vs Positive)	3.69	1.17–11.63	0.026	1.73	0.14–21.27	0.670
HER2 status (2+/FISH-negativity vs 0/1+)	4.66	1.02–21.26	0.047	5.56	1.03–30.06	0.046
Adjuvant chemotherapy (AC/TC vs AC–T)	1.01	0.33–3.13	0.989	2.09	0.50–8.69	0.309
Endocrine therapy (Yes vs No)	0.24	0.07–0.78	0.018	0.29	0.02–3.66	0.338
Radiotherapy (Yes vs No)	1.68	0.51–5.58	0.397	0.97	0.23–4.13	0.964

Abbreviations: DFS, disease-free survival; HR, hormone receptor; FISH, fluorescent in situ hybridization; AC, anthracycline plus cyclophosphamide; TC, taxane plus cyclophosphamide; AC–T, anthracycline plus cyclophosphamide followed by taxane; CI, confidence interval.

associations with DFS. In multivariate analysis, HER2 2+/FISH-negativity was the only independent predictor for unfavorable DFS (hazard ratio 5.56; 95% CI 1.03–30.06; *P*=0.046).

Disease-free survival was significantly worse among patients with HER2 2+/FISH-negativity than among those with HER2 0 or 1+ (Log rank test, *P*=0.029; Figure 1a). Exploratory subgroup analysis according to HR status indicated that, in both HR positive (Log rank test, *P*=0.052; Figure 1b) and HR negative (Log rank test, *P*=0.125; Figure 1c) subgroups, tumors with HER2 2+/FISH-negativity had shorter DFS compared with those with HER2 0 or 1+, and survival differences showed a tendency toward statistical significance.

Discussion

Although little research reported that HER2 2+/ISH-negativity had associations with unfavorable survival in younger breast cancer, no evidence can be identified in older individuals. In this cohort of older patients with HER2-negative /high-risk breast cancer undergoing standard adjuvant chemotherapy, survival analyses suggested a significant negative impact of HER2 2+/FISH-negativity on prognosis. To our knowledge, our study first reported the prognostic significance of HER2 2+/FISH-negativity for breast cancer in the older population.

Despite the prevalence of breast cancer in older individuals, clinical trials traditionally included 15% or less of patients older than 65 years, and solid trial-level evidence for clinical decisions is relatively sparse.[6–8] Additionally, the heterogeneity and frailty of older patients makes treatment decisions full of complexity, particularly in the application of adjuvant chemotherapy. In routine practice, extrapolation of therapeutic principles from other age populations occurs frequently, and undertreatment does exist.[6–8] Real-world evidence has indicated an inferior treatment for older patients with breast cancer even in high-risk disease, which might be the reason for poorer relative survival compared with younger counterparts.[28,29] However, fit older individuals can tolerate and benefit from standard chemotherapy.[6–8] Therefore, we analyzed the clinicopathological data of older patients with breast cancer in our center, and intended to report the real-world prognosis of high-risk patients completing standard adjuvant chemotherapy. Over a median follow-up of 46 months, 9.9% of this high-risk population underwent local recurrence or distant metastasis, suggesting a generally favorable outcome after standard adjuvant chemotherapy.

For older patients, breast cancer with high risk of recurrence and/or metastasis can benefit from chemotherapy. Despite substantial research on risk factors for prognosis in younger patients, precise high-risk population of breast cancer in older patients has been poorly investigated without consensus. Based on previous related investigations and established risk factors for younger patients, for defining high-risk disease in our study, parameters about tumor stage and

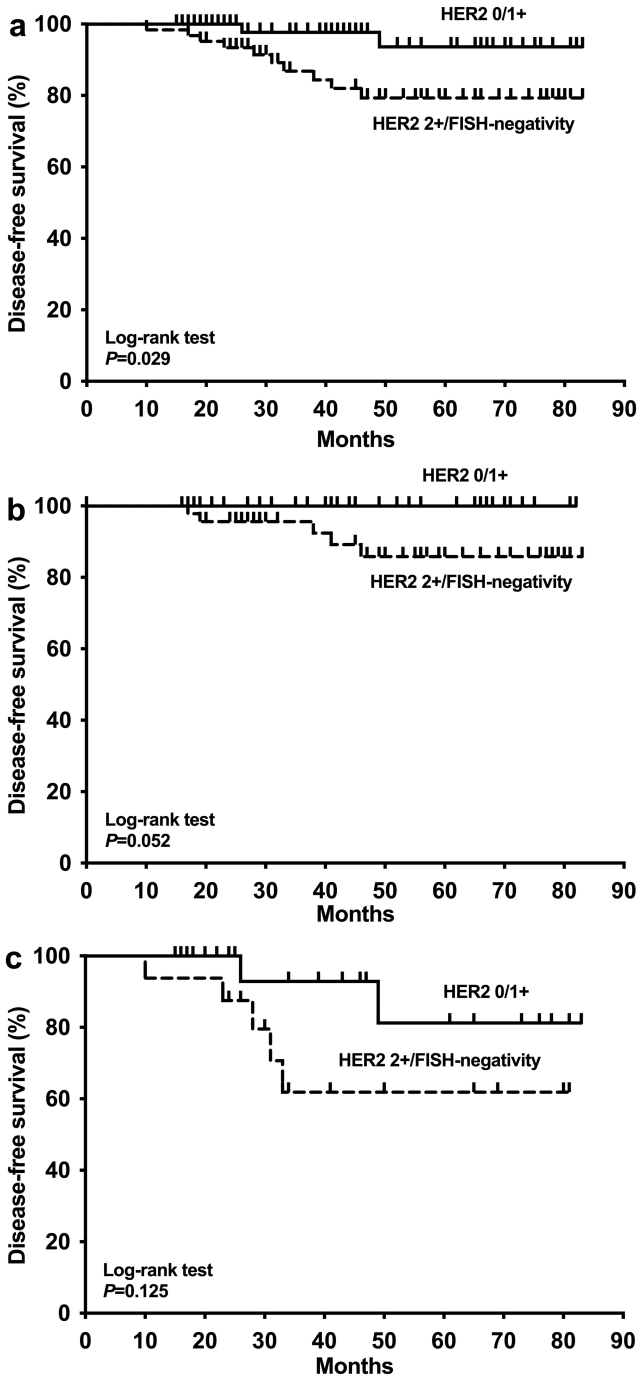

Figure 1 DFS curves of patients with HER2 2+/FISH-negativity versus HER2 0/1+ in the (**a**) entire population, (**b**) HR-positive subgroup, and (**c**) HR-negative subgroup.
Abbreviations: DFS, disease-free survival; FISH, fluorescent in situ hybridization; HR, hormone receptor.

aggressive biological behavior were taken into account.[20,22–24] In younger counterparts with HR-positive/HER2-negative disease, gene expression profiling has been proved to be an important tool for determining prognosis and survival benefit from adjuvant chemotherapy.[30] Nonetheless, due to insufficient evidence in older population, results of gene expression signatures were not judged as risk factors in our study.[31]

The early CALGB 49907 study demonstrated the survival benefit of AC,[20] and subsequent research suggested that TC avoided the cardiotoxicity of anthracyclines[32] with a superior survival benefit, compared with AC.[12] Besides, evidence also supports that AC-T can be considered for high-risk patients.[7,33] AC, TC or AC-T can be considered in the adjuvant

treatment based on individual risks and benefits.[7,34] Taxanes and/or anthracyclines are still the cornerstone of adjuvant chemotherapy for breast cancer in older patients. Therefore, standard adjuvant chemotherapy in the present study was restricted to taxane- and/or anthracycline-based regimens, and completing predetermined cycles of chemotherapy with a relative dose intensity of 85% or more was compulsory, which was crucial for achievement of expected survival benefit and accuracy of prognostic analysis.

HER2 status carries a pivotal prognostic and therapeutic significance in breast cancer. Survival outcomes of HER2-positive disease, defined as IHC 3+ or 2+ with gene amplification by ISH, have been significantly improved by targeted therapy, such as trastuzumab, pertuzumab, and antibody-drug conjugates (ADC).[35] HER2-negative disease consists of carcinomas with different degrees of HER2 expression, the highest end of which is HER2 2+ without gene amplification. Long-standing hypothesis exists that greater signaling without gene amplification can also lead to an aggressive biological behavior. Further research indicated that, even in the HER2-low category, HER2 2+/ISH-negative carcinomas had a distinct distribution of intrinsic subtypes and gene expression profiles.[36,37] In younger population, several studies have reported a correlation between HER2 2+/ISH-negativity and adverse histopathological characteristics.[17–19] All these evidence supports that HER2 2+/ISH-negativity might be biologically different with a possible adverse influence on survival.

In younger population, limited evidence has shown that the survival of patients with HER2 2+/ISH-negativity is worse than that of HER2 0 or 1+ patients.[17–19] Nevertheless, previous investigations had several limitations and unsolved issues. Firstly, and most importantly, none of these researches was specially designed for older patients, and the cohorts consisted of younger patients mostly with no subgroup analyses for older individuals. Prognostic significance of HER2 2+/ISH-negativity in older patients with HER2-negative breast cancer has been unknown. Furthermore, despite consistent unfavorable impact on prognosis for HER2 2+/ISH-negativity in HR-positive/HER2-negative disease, contradictory results existed about its prognostic significance in HR-negative/HER2-negative subtype. Lastly, chemotherapy in these studies has not been standardized, which might have an adverse and uncontrolled influence on survival analyses. Thus, we systemically studied the associations of HER2 2+/FISH-negativity with long-term survival in older patients undergoing standard adjuvant chemotherapy. Univariate and multivariate analyses indicated that HER2 2+/FISH-negativity was the only independent predictor of poorer DFS. Our study suggests that HER2 2+/FISH-negativity has an adverse prognostic significance in older patients with high-risk breast cancer, and standard adjuvant chemotherapy might be insufficient for patients with HER2 2+/FISH-negativity. Escalating systemic treatment, such as ADC, can be verified in subsequent studies for fit older patients with HER2 2+/FISH-negativity. In addition, HER2 2+/FISH-negativity consistently predicted shorter DFS in the exploratory subgroup analyses of both HR-positive and HR-negative subtypes. However, due to the limitation of sample size, the results of subgroup analysis did not reach statistical significance. Future studies should focus on the prognostic significance of HER2 2+/FISH-negativity in carcinomas with different HR status.

We acknowledge that the current study has several limitations. Firstly, the relatively small number of patients included may affect statistical analyses, particularly in the subgroup analysis, which did not show statistical significance. In real-world practice, receiving standard chemotherapy remains uncommon for older patients with breast cancer. For standardizing adjuvant chemotherapy, strict inclusion criteria of our study resulted in a limited sample size but a relatively homogenous population. Secondly, the retrospective design and the limited follow-up of our study emphasize the need for further prospective studies with longer periods of observation. Thirdly, as the aim of the present study was to investigate the associations of HER2 2+/FISH-negativity with survival, we compared HER2 2+/FISH-negativity with HER2 0 or 1+. The prognostic impact of HER2 0, 1+, or 2+/FISH-negativity separately needs future research with a larger sample size.

Conclusions

HER2 2+/FISH-negativity is an independent predictor of unfavorable prognosis after standard adjuvant chemotherapy in older patients with HER2-negative and high-risk breast cancer. Our findings may help predict survival outcomes and guide the individualized decision-making of adjuvant treatment in HER2-negative older population.

Data Sharing Statement

The data presented in the current study are available from the corresponding author upon reasonable request.

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Disclosure

The authors report no conflicts of interest in this work.

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