Clinical information and management status of *de novo* stage IV breast cancer patients: a Chinese multicenter investigation (CSBrS-002)

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Abstract

Background: Although *de novo* stage IV breast cancer is so far incurable, it has entered an era of individualized treatment and chronic disease management. Based on systemic treatment, whether the surgical resection of primary or metastatic foci of *de novo* stage IV breast cancer can bring survival benefits is currently controversial. We aimed to explore the clinicopathological factors and current status of the management of *de novo* stage IV breast cancer in China to provide a reference for clinical decisions.

Methods: Based on the assistance of Chinese Society of Breast Surgery, a retrospective study was conducted to analyze the clinical data of patients with *de novo* stage IV breast cancer in 33 centers from January 2017 to December 2018. The relationship between basic characteristic (age, menstrual status, family history, reproductive history, pathological type, estrogen receptor [ER] status, progesterone receptor [PR] status, human epidermal growth factor receptor 2 [HER2] status, Ki-67 percentage, and molecular subtype), and metastasis sites (lung metastasis, liver metastasis, and bone metastasis) was examined by Pearson Chi-square tests.

Results: A total of 468 patients with *de novo* stage IV breast cancer were enrolled. The median age of the enrolled patients was 51.5 years. The most common pathological type of primary lesion was invasive carcinoma (97.1%). Luminal A, luminal B, HER2 overexpressing, and triple-negative subtypes accounted for 14.3%, 51.8%, 22.1%, and 11.8% of all cases, respectively. Age, PR status, and HER2 status were correlated with lung metastasis ($\chi^2 = 6.576$, 4.117, and 8.643 and $P = 0.037$, 0.043, and 0.003, respectively). Pathological type, ER status, PR status, and molecular subtype were correlated with bone metastasis ($\chi^2 = 5.117$, 37.511, 5.224, and 11.603 and $P = 0.024$, <0.001, 0.022, and 0.009, respectively). Age, PR status, HER2 status, Ki-67 percentage, and molecular subtype were correlated with liver metastasis ($\chi^2 = 11.153$, 13.378, 10.692, 21.206, and 17.684 and $P = 0.004$, <0.001, 0.001, <0.001, and 0.001, respectively). Combined treatment with paclitaxel and anthracycline was the most common first-line chemotherapy regimen for patients with *de novo* stage IV breast cancer (51.7%). Overall, 91.5% of patients used paclitaxel-containing regimens. Moreover, 59.3% of hormone receptor-positive patients underwent endocrine therapy.

Conclusions: In 2018, 1.07% of patients from all studied centers were diagnosed with *de novo* stage IV breast cancer. This study indicated that 95.1% of patients received systemic therapy and 54.2% of patients underwent surgical removal of the primary lesion in China.

Keywords: *De novo* stage IV breast cancer; Metastatic site; Systemic therapy; Multicenter investigation; Chinese Society of Breast Surgery

Introduction

Breast cancer is the most frequent malignancy among females worldwide.[1] In China, breast cancer accounts for approximately 12.2% of all cancer diagnoses and 9.6% of all cancer-related deaths.[2] According to the eighth edition of the primary tumor, lymph node, and metastasis classification system of the American Joint Commission of Cancer, stage IV breast cancer is defined as breast cancer with any T stage, any N stage, and an M stage of M1. M1 is defined as metastasis from the breast and axilla to distant sites.[3] Approximately 5% to 10% of new breast cancer cases are diagnosed as *de novo* stage IV breast cancer, characterized by metastasis present at diagnosis, and the 5-

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year survival is approximately 20%.[4-6] In the United States, approximately one-quarter of stage IV breast cancer cases are diagnosed as *de novo* disease.[7] Accurate diagnosis is essential for *de novo* stage IV breast cancer patients, as it provides the basis for appropriate treatment. It is recommended to evaluate clinical information and pathological features before systemic treatment.[8] It is also recommended that rebiopsy of relapsed and metastatic lesions be performed to evaluate their molecular subtypes for guiding clinical treatment.[9,10] However, clinical pathological data on a larger scale have not been investigated among Chinese *de novo* stage IV breast cancer patients. Meanwhile, the diagnostic information is not standardized and has not been evaluated in China before.

Clinicopathological data can promote a better understanding of biological behavior, especially metastatic patterns of stage IV breast cancer. There are many factors that determine disease monitoring and influence the therapeutic efficacy of drugs targeting stage IV breast cancer, one of which is the molecular subtype.[11] Molecular subtypes are also correlated with metastatic patterns, recurrence, and survival after distant metastasis.[12-14] This study includes a preliminary analysis of the significance and impact of molecular subtype on the site of distant metastasis in Chinese *de novo* stage IV breast cancer patients.

De novo stage IV breast cancer is a highly heterogeneous disease and is considered incurable. Thus, the primary goals of treatment are to alleviate the clinical symptoms, improve the quality of life, and prolong the survival time of patients.[15] Systemic therapy is the primary treatment of stage IV breast cancer, including endocrine therapy, chemotherapy, and targeted therapy. There is still no standard recommendation for the management of stage IV breast cancer after multiline treatments. Prospective studies have yielded conflicting results, regarding whether primary tumor surgery contributes to survival benefit. Furthermore, controversy still exists about which subgroup of *de novo* stage IV breast cancer patients should undergo locoregional treatment, such as surgical resection of the primary tumor.[16] In China, these issues also remain unclear.[17] Therefore, investigating the management status of *de novo* stage IV breast cancer patients is of important reference value for clinical decision-making.

Therefore, this study descriptively analyzed the data of *de novo* stage IV breast cancer patients from 2017 to 2018, with the support of Chinese Society of Breast Surgery (CSBrS) by using a unified design electronic questionnaire to provide a reference for clinical decision-making for *de novo* stage IV breast cancer.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of the First Affiliated Hospital of China Medical University (No. AF-SOP-07-1.1-01). This study was performed in accordance with the guidelines provided by the World Medical Association *Declaration of Helsinki* on Ethical Principles for Medical Research Involving Humans. Informed consents were obtained from all the enrolled patients.

Clinical data

The CSBrS collected clinical data from 468 *de novo* stage IV breast cancer patients hospitalized from January 2017 to December 2018. Included patients met the following inclusion criteria: initial diagnosis of metastatic breast cancer; complete clinical and pathological records; and no other malignant tumors. This study enrolled 33 membership centers of the CSBrS, distributed in 22 major cities in China. Membership centers are listed in the acknowledgment section, according to the numbers of patients.

Electronic questionnaire

The CSBrS designed a standard electronic questionnaire. The survey covered 11 categories and 51 sub-items. Some of the included categories were basic features, primary diagnosis, primary lesion, metastasis discovery time, and so on. For example, there were nine items under the primary lesions category, including biopsy method, pathological type, histological grade, estrogen receptor (ER), progesterone receptor (PR), Ki-67, human epidermal growth factor receptor 2 (HER2), fluorescence *in situ* hybridization results, and molecular types. The questionnaire is shown in Supplementary File 1, http://links.lww.com/CM9/A653.

Data collection

Each center collected data from their Hospital Information System in accordance with the questionnaire. The CSBrS summarized all the data and performed quality control, which included the input format and content. Patients who did not meet the requirements were re-analyzed or excluded. Finally, the CSBrS completed a standardized database. In this study, 150 patients were hospitalized in 2017, while 318 patients were hospitalized in 2018.

Statistical analysis

Statistical analysis of the data was performed using SPSS 21.0 statistical software (SPSS Inc., Chicago, IL, USA). The difference between the groups was examined by Pearson Chi-square tests. Survival probabilities were judged by the Kaplan-Meier and assessed by a log-rank test. All data were considered statistically significant when $P < 0.05$.

Results

Patient characteristics

In 2018, 318/29675 (1.07%) of breast cancer patients in 33 centers were diagnosed with *de novo* stage IV breast cancer. Eighty-four (18.0%) patients were diagnosed at the age of 40 years or below; 262 (56.0%) patients were diagnosed between the ages of 41 and 59 years; 122 (26.1%) were diagnosed over 60 years. The mean age was 51.6 ± 11.8 years; the minimum age was 24 years, and the maximum age was 86 years. Eleven percent of patients had

a family history of malignancy. For immunohistochemical indicators, Ki-67 was classified according to the guidelines set forth by Chinese Society of Clinical Oncology Breast Cancer 2019 (CSCO BC 2019). In this study, only 16.1% had low Ki-67 expression. Luminal A, luminal B, HER2 overexpressing, and triple-negative subtypes accounted for 14.3%, 51.8%, 22.1%, and 11.8% of the total, respectively. The most common pathological type of primary lesion was invasive carcinoma, accounting for 97.1% of all primary lesions. The follow-up information we have collected so far is relatively limited. A total of 148 patients had information about follow-up. The mean follow-up period was 16.3 months. The demographic and pathological features of the *de novo* stage IV breast cancer patients are summarized in Table 1.

Diagnosis of de novo stage IV breast cancer

For the diagnosis of primary lesions, ultrasound combined with molybdenum target (mo-target) mammography was the most common primary imaging diagnosis method, accounting for 57.3% of cases (63/110, 110 cases had clear imaging diagnosis). Core needle biopsy was the most common primary pathological diagnosis method, accounting for 99.3% of cases (143/144, 144 cases had clear pathological diagnosis). For the diagnostic methods of metastasis, among the 165 patients with bone metastasis who had clear diagnostic modes, 160 patients (97.0%) were diagnosed by whole-body bone scintigraphy and computerized tomography (CT). A total of 120 patients with visceral metastasis had clear records of diagnostic modes. Visceral metastasis was mostly diagnosed by magnetic resonance imaging combined with CT (60 patients, 50.0%) or by positron emission tomography-computed tomography (38 patients, 31.7%). Among the 468 patients, 51 patients (10.9%) had a definite pathologic diagnosis of metastatic foci, among which nine patients (17.7%) had different molecular subtypes between metastatic foci and primary foci.

Table 1: The demographic and pathological features of the patients with *de novo* stage IV breast cancer.

Items	*n* (%)
Age ($n = 468$)	
≤40 years	84 (18.0)
41–59 years	262 (56.0)
≥60 years	122 (26.0)
Menstrual status ($n = 459$)	
Post-menopausal	222 (48.4)
Menopause	237 (51.6)
Family history ($n = 462$)	
Breast cancer	14 (3.0)
Other malignancy	37 (8.0)
None	411 (89.0)
Reproductive history ($n = 430$)	
Yes	417 (97.0)
No	13 (3.0)
ER/PR ($n = 453$)	
Positive/positive	254 (56.1)
Positive/negative and negative/positive	65 (14.3)
Negative/negative	134 (29.6)
HER2 expression ($n = 416$)	
Negative	246 (59.8)
Positive	170 (40.2)
Ki-67 percentage ($n = 448$)	
>30%	208 (46.4)
15%–30%	168 (37.5)
<15%	72 (16.1)
Molecular subtype ($n = 440$)	
Luminal A	63 (14.3)
Luminal B	228 (51.8)
HER2+	97 (22.1)
TNBC	52 (11.8)
Pathological type ($n = 448$)	
DCIS	13 (2.9)
Infiltrative cancer	435 (97.1)

DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor-2; PR: Progesterone receptor; TNBC: Triple-negative breast cancer.

Relationship of basic characteristics and metastasis types

Age ($\chi^2 = 6.576$, $P = 0.037$), PR status ($\chi^2 = 4.117$, $P = 0.042$), and HER2 status ($\chi^2 = 8.643$, $P = 0.003$) were correlated with lung metastasis. Pathological type ($\chi^2 = 5.117$, $P = 0.024$), ER status ($\chi^2 = 37.511$, $P < 0.001$), PR status ($\chi^2 = 5.224$, $P = 0.022$), and molecular subtype ($\chi^2 = 11.603$, $P = 0.009$) were correlated with bone metastasis. Age ($\chi^2 = 11.153$, $P = 0.004$), PR ($\chi^2 = 13.378$, $P < 0.001$), HER2 ($\chi^2 = 10.692$, $P = 0.001$), Ki-67 percentage ($\chi^2 = 21.206$, $P < 0.001$), and molecular subtype ($\chi^2 = 17.684$, $P = 0.001$) were correlated with liver metastasis. Compared with other molecular types, hormone receptor (HR)-negative/HER2-positive had a higher proportion of liver metastasis (44.3%). Luminal B type had the highest proportion of bone metastasis (52.6%). Compared with other subtypes, patients with triple-negative breast cancer (TNBC) were less likely to have bone metastasis (26.9%), and this difference was statistically significant (TNBC *vs.* luminal A, $\chi^2 = 5.165$, $P = 0.023$; TNBC *vs.* luminal B, $\chi^2 = 11.215$, $P = 0.001$; TNBC *vs.* HER2, $\chi^2 = 4.342$, $P = 0.037$). There was no significant difference in pulmonary metastasis among breast cancer subtypes ($\chi^2 = 1.393$, $P = 0.707$) [Table 2].

Management status of de novo stage IV breast cancer patients

The multicenter retrospective analysis of patients who underwent primary tumor resection after they were diagnosed with *de novo* stage IV breast cancer was 241/445 (54.2%) from 2017 to 2018. The detailed operation types in patients who received surgery were modified radical mastectomy, breast-conserving surgery, total mastectomy, local mastectomy, and other types that removed the primary tumor. To investigate the different effects of different treatments on *de novo* stage IV breast cancer patients, 148 patients with follow-up information were divided into two groups. Eighty-one (54.7%) patients accepted systemic therapy alone, while 67 (48.3%) patients received primary tumor resection and systemic therapy. We performed Kaplan-Meier survival analysis. Overall survival (OS) was defined from the date of

Table 2: Relationship between basic characteristics and metastasis sites of patients with *de novo* stage IV breast cancer.

Factors	Lung metastasis			Bone metastasis			Liver metastasis		
	Y	*N*	*P*	*Y*	*N*	*P*	*Y*	*N*	*P*
Age ($n = 468$)			0.037			0.292			0.004
≤40 years	60 (49.2)	62 (50.8)		60 (49.2)	62 (50.8)		42 (34.4)	80 (65.6)	
40–60 years	98 (37.4)	164 (62.6)		114 (43.5)	148 (56.5)		58 (22.1)	204 (77.9)	
≥60 years	28 (33.3)	56 (66.7)		44 (52.4)	40 (47.6)		32 (38.1)	52 (61.9)	
Menstrual status ($n = 459$)			0.710			0.715			0.068
Post-menopausal	89 (40.1)	133 (59.9)		104 (46.8)	118 (53.2)		55 (24.8)	167 (75.2)	
Menopause	91 (38.4)	146 (61.6)		107 (45.1)	130 (54.9)		77 (32.5)	160 (67.5)	
Family history ($n = 462$)			0.925			0.500			0.888
Malignancy	20 (39.2)	31 (60.8)		26 (51.0)	25 (49.0)		15 (29.4)	36 (70.6)	
None	164 (39.9)	247 (60.1)		189 (46.0)	222 (54.0)		117 (28.5)	294 (71.5)	
Reproductive history ($n = 430$)			0.071			0.262			0.834
Yes	168 (40.3)	249 (59.7)		194 (46.5)	223 (53.5)		124 (29.7)	293 (71.3)	
No	2 (15.4)	11 (84.6)		4 (30.8)	9 (69.2)		3 (23.1)	10 (76.9)	
Pathological type ($n = 448$)			0.275			0.024			0.120
DCIS	7 (53.8)	6 (46.2)		2 (15.4)	11 (84.6)		6 (46.2)	7 (53.8)	
Infiltrative cancer	169 (38.9)	266 (61.1)		205 (47.1)	230 (52.9)		116 (26.7)	319 (73.3)	
ER ($n = 454$)			0.329			<0.001			0.205
Positive	114 (41.5)	161 (58.5)		159 (57.8)	116 (42.2)		71 (25.8)	204 (74.2)	
Negative	66 (36.9)	113 (63.1)		51 (28.5)	128 (71.5)		56 (31.3)	123 (68.7)	
PR ($n = 454$)			0.042			0.022			<0.001
Positive	83 (31.2)	183 (68.8)		135 (50.8)	131 (49.2)		57 (21.4)	209 (78.6)	
Negative	76 (40.4)	112 (59.6)		75 (39.9)	113 (60.1)		70 (37.2)	118 (62.8)	
HER2 ($n = 416$)			0.003			0.507			0.001
Positive	81 (47.6)	89 (52.4)		78 (45.9)	92 (54.1)		63 (37.1)	107 (62.9)	
Negative	82 (33.3)	164 (66.7)		121 (49.2)	125 (50.8)		55 (22.4)	191 (77.6)	
Ki-67 percentage ($n = 448$)			0.254			0.247			<0.001
>30%	85 (40.9)	123 (59.1)		91 (43.8)	117 (56.2)		79 (38.0)	129 (62.0)	
15%–30%	69 (41.1)	99 (58.9)		85 (50.6)	83 (49.4)		34 (20.2)	134 (79.8)	
<15%	22 (30.6)	50 (69.4)		29 (40.3)	43 (59.7)		11 (15.3)	61 (84.7)	
Molecular subtype ($n = 440$)			0.707			0.009			0.001
Luminal A	22 (34.9)	41 (65.1)		30 (47.6)	33 (52.4)		9 (14.3)	54 (85.7)	
Luminal B	91 (39.9)	137 (60.1)		120 (52.6)	108 (47.4)		54 (23.7)	174 (76.3)	
HER2	39 (40.2)	58 (59.8)		43 (44.3)	54 (55.7)		40 (41.2)	57 (58.8)	
TNBC	17 (32.7)	35 (67.3)		14 (26.9)	38 (73.1)		18 (34.6)	34 (65.4)	

Data were shown as *n* (%). Y: Yes; N: No; DCIS: Ductal carcinoma *in situ*; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor-2; PR: Progesterone receptor; TNBC: Triple-negative breast cancer.

Table 3: First-line chemotherapy for *de novo* stage IV breast cancer ($n = 387$).

Chemotherapy regimen	*n* (%)
Anthracyclines + paclitaxel	221 (51.7)
Paclitaxel	61 (15.7)
Paclitaxel + platinum	38 (9.8)
Capecitabine + paclitaxel	34 (8.9)
Cyclophosphamide + anthracyclines	21 (5.4)
Others	12 (3.1)

diagnosis to the date of metastatic breast cancer-related death. The OS between these two groups was not significantly different ($P = 0.250$, Supplementary Figure 1, http://links.lww.com/CM9/A652).

In this study, 445 patients (95.1%) received systemic therapy. Among them, a total of 387 patients (82.7%) were treated with a variety of chemotherapy regimens. Paclitaxel was the dominant first-line chemotherapy drug for *de novo* stage IV breast cancer, with 91.5% receiving a paclitaxel-containing regimen. Paclitaxel combined with anthracycline was the most frequently used combined chemotherapy regimen (51.7%) for *de novo* stage IV breast cancer patients [Table 3]. Regarding targeted therapy for *de novo* stage IV breast cancer, among the 164 *de novo* stage IV breast cancer patients with positive HER2, 138 patients received targeted therapy, accounting for 84.2% of all patients. Approximately 85.5% of HER2 targeted therapy regimens used trastuzumab. Other regimens of HER2-targeted therapy were trastuzumab and pertuzumab, trastuzumab and lapatinib, and trastuzumab and pyrotinib. Regarding endocrine therapy for *de novo* stage IV breast cancer, 319 patients were ER- and/or PR-positive, 153 of whom (48.0%) received endocrine therapy.

Discussion

The severity of the primary malignancy was high in *de novo* stage IV breast cancer, which can be reflected in the

low rate of Ki-67 expression (16.1%). It is of clinical and biological significance to understand preferred distant metastasis sites. The seed and soil hypothesis is well-known to demonstrate that breast cancer spreads in a non-random and organotropic metastatic pattern.[18] HR−/HER2+ and HR−/HER2− patients present more visceral metastases, including to the liver and lung.[13,14] Similar to previous studies, this study indicated that HR-negative/HER2-positive patients had a higher proportion of liver metastasis than others.[13,19,20] In this study, only TNBC had a low probability of bone metastasis, which was consistent with a previous study.[13] HR-positive patients are more likely to have bone metastases.[21,22] Moreover, patients with bone metastases may have a longer OS than those with visceral metastases.[23,24] The lung metastasis results were similar to the findings of a surveillance, epidemiology, and end results study involving 243,896 patients, which showed no statistically significant difference in the probability of lung metastasis among molecular subtypes.[19] A 10-year retrospective analysis of 390 cases in China showed a high rate of lung metastasis in HER2-positive and TNBC patients, but not in luminal-type patients. A study indicated that patients with TNBC and HR−/HER2+ had a higher incidence of lung metastasis than patients with other breast cancer subtypes.[20] There may be several reasons for the difference. Breast cancer is typically divided into the following subtypes: HR+/HER2+, HR−/HER2+, HR+/HER2−, and TNBC; however, this study divided breast cancer into luminal A, luminal B, HER2-positive, and TNBC. Information about the metastatic involvement of specific organ sites was only collected at the time of initial presentation, and there was no longitudinal follow-up data to document subsequent organs affected; however, in this study, metastatic patterns were retrospectively surveyed, with origin and subsequent metastatic organ sites considered.

The identification of factors associated with tumor spread to specific organs has been the subject of decades of research. To predict the preferential dissemination of a tumor to a distant site, a predictive model based on clinicopathological factors and multigenic assays, and some other possible methods with sufficient sample sizes can be used; these methods are considered to be effective ways to provide more valuable evidence and precise predictions.

Is local surgery necessary for *de novo* stage IV breast cancer? In this study, the relationship between surgical removal surgery of the primary tumor and survival among *de novo* stage IV breast cancer patients is inconclusive and is currently being assessed. Retrospective clinical studies have shown that resection of the primary tumor brought about a significant increase in the survival rates.[7,25,26] However, prospective studies have yielded conflicting results as to whether the local surgery itself contributes to survival benefit. The TBCRC013 prospective study suggested that the removal of a single lesion hardly affected the outcome.[27] The Turkey MF07-01 phase III randomized prospective study suggested that tumor reduction by surgery may have a positive effect on the follow-up comprehensive treatment.[28,29] A prospective study from India, the TMH/153/2004 study (NCT00193778), reported no evidence to suggest that locoregional treatment of the primary tumor affects OS.[5] Randomized clinical trials are now under way but have been slow to accrue and report.[30,31] In the future, we can also assess characteristics associated with surgical treatment and determine the impact on survival in women with stage IV breast cancer.

Although there are many combined chemotherapy regimens, it has not been definitely concluded whether one regimen is significantly better than another. Regarding the efficacy of first-line chemotherapy regimens, the regimen with paclitaxel was significantly better than the regimen without paclitaxel in the treatment of *de novo* stage IV breast cancer.[32] We found that 48.0% of HR-positive patients received endocrine therapy. These data can be discussed after determining whether endocrine therapy is used for first-line treatment or maintenance treatment. For HER2-positive stage IV breast cancer, National Comprehensive Cancer Network recommends anti-HER2 treatment combined with chemotherapy or anti-HER2 treatment alone.[9] Compared with chemotherapy alone, trastuzumab combined with chemotherapy increased the objective response rate (50% *vs.* 32%, $P < 0.001$) and significantly prolonged the time to progression (7.4 *vs.* 4.6 months, $P < 0.001$) and OS.[33]

We need to be clear about limitations in our study and strive to improve information for the future. First, the population-based design could include errors in data reporting; the pathologic data were collected from different local pathology laboratories and were not centrally reviewed. Second, the OS between surgery group and non-surgery group in this study was not significantly different. We need to further expand the follow-up data, record the sites of metastasis, and extend the follow-up time. Finally, we currently do not collect information on other sites of metastases, such as brain, which could assist in more specific prognostic assessment of the other metastases group.

To conclude, 1.07% of patients in the 33 studied centers were diagnosed with *de novo* stage IV breast cancer in China. This study investigated the characteristics, pathological information, and management strategies of *de novo* stage IV breast cancer in China. The methods for evaluating metastatic foci are still unsatisfactory. Primary foci information is used to evaluate metastatic foci in most cases. It is still unknown whether certain sub-groups of *de novo* stage IV breast cancer patients can benefit from surgery in China. Descriptive analysis of follow-up history and subsequent follow-up information is expected to provide a vital reference for the multidisciplinary management of *de novo* stage IV breast cancer patients.

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Conflict of Interest

None.

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