Original Article

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Pure Mucinous Breast Carcinoma With a Favorable Tumor Biology and Clinical Outcomes

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ABSTRACT

Objective: A few studies suggest that mucinous breast carcinoma (MBC) is a rare breast carcinoma with good prognostic features. Therefore, the aim of this study was to evaluate biological features and clinicopathological characteristics of pure mucinous breast carcinoma (PMBC) to determine clinical outcome in PMBC.

Materials and Methods: The data of 87 patients diagnosed with PMBC between November 2004 and February 2022 were retrospectively analyzed in terms of clinicopathological and demographic characteristics, management, and outcome.

Results: The majority of the patients in this study were female, with a median (range) age of 63 (28–90) years. Out of 87 patients, 60 had breast conserving surgery, 27 had a mastectomy, 58 had sentinel lymph node biopsy (SLNB), and 24 had axillary dissection due to a positive SLNB or clinical axilla. Due to age and comorbidities, five patients were not suitable for axillary surgery. The median largest tumor diameter was 23 (5–100) mm. Only 23 patients (26.4%) received adjuvant chemotherapy, whereas almost all patients received hormone therapy. The median duration of follow-up was 53 (6–207) months. There was no local or systemic recurrence in any of the patients. Only 10 patients (11.5%) died from non-cancer causes during the follow-up and treatment period. In this study, tumor diameter was significantly higher in grade II/III tumors (p = 0.039) and in patients under the age of 50 (p = 0.027). Furthermore, lymph node metastasis was statistically significantly more likely in patients under the age of 50 (60% *versus* 40%, p = 0.013). Patients who had not received chemotherapy or radiotherapy tended to be older than 50 years (p = 0.002).

Conclusion: In this study, the majority of patients were in the luminal subgroups with excellent prognosis and low incidences of lymph node metastasis. As a result, PMBC has favorable tumor biology. We believe that minimal axillary surgery would be the most appropriate approach during patient treatment, due to the low rate of lymph node involvement and favorable prognosis in PMBC patients.

Keywords: Mucinous carcinoma; molecular subtype; prognosis

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Key Points

- Few studies suggested that mucinous breast carcinoma is a rare breast carcinoma with good prognostic factors. Therefore, in this study, biologic features and clinicopathological characteristics of pure mucinous breast carcinoma were investigated to determine its clinical outcome.

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Introduction

Mucinous breast carcinoma (MBC) is relatively uncommon subtype of breast cancer, representing about 2% of all invasive breast cancers (1). In general, MBC presents at a mean age of 65 years, with 1% incidence in women under the age of 35 years. MBC patients are generally diagnosed through physical examination or mammography (2). MBC is characterized with the presence of tumor cells floating in extracellular mucin pools. Based on mucin contents, MBC is further divided into pure and mixed subgroups. Pure mucinous breast carcinoma (PMBC) contains a higher content of mucin than mixed mucinous breast carcinoma (MMBC). In this study, we considered tumors with more than 90% mucin content to be PMBC and less than 90% mucin contents to be MMBC (3). MBC patients have some features that differ from those of patients with invasive ductal carcinoma not otherwise specified. MBC has a lower incidence of nodal involvement, favorable histological grade (HG) and higher estrogen receptor (ER) and progesterone receptor (PR) expression (4). Breast carcinoma is a heterogeneous tumor with many clinical features that could be prognostic factors for patients. Despite the good prognosis of MBC, its clinical, histological, immunohistochemical characteristics and prognostic factors are still debatable. The purpose of this study was to report the last 18-year experience of the Department of Breast Surgery of the Istanbul Faculty of Medicine of Istanbul University regarding MBC with its histological and immune-histochemical characteristics and patient outcomes.

Materials and Methods

This study was based on an analysis of a large mono-institutional series of breast cancer patients treated in a high-volume reference center with widely standardized treatment and management. A multidisciplinary team had discussed each case individually after surgery, and all decisions about adjuvant treatment were made at these meetings.

Patient Selection and Follow-up

The study population was constituted at the Department of General Surgery, Breast Surgery Unit, and consisted of 87 female patients who had undergone surgical operations in the General Surgery Department. In addition, the PMBC diagnosis was assumed retrospectively. From the prospectively collected data between November 2004 and February 2022, we analyzed patients' demographics and pathologic features.

All cases' histological types were strictly controlled, and cases other than PMBC were excluded. Clinical and pathological factors, such as tumor size, surgical procedure, presence of loco-regional recurrence or distant metastasis, pathological characteristics, nodal staging, adjuvant treatment, and survival were analyzed. Personal contact with patients, including routine correspondence and telephone calls, was used to follow the patients. Follow-ups were performed at Istanbul University's Department of General Surgery, Breast Surgery Unit, every three months for the first two years, every six months for the next two years, and once a year after that. Patients were treated with either mastectomy or lumpectomy and axillary lymph node dissection (ALND) or sentinel lymph node biopsy (SLNB) with local radiotherapy. After completion of the surgery, adjuvant treatments were administered as indicated based on international guidelines.

SLNB Method

Intraoperative visual blue dye (isosulfan blue) detection procedure was used. A frozen section procedure was employed, so if neoplasia was detected in the lymph node, a further lymph node dissection was performed. ALND was defined as a dissection of at least anatomical levels I and II including at least ten nodes, as shown in Figure 1.

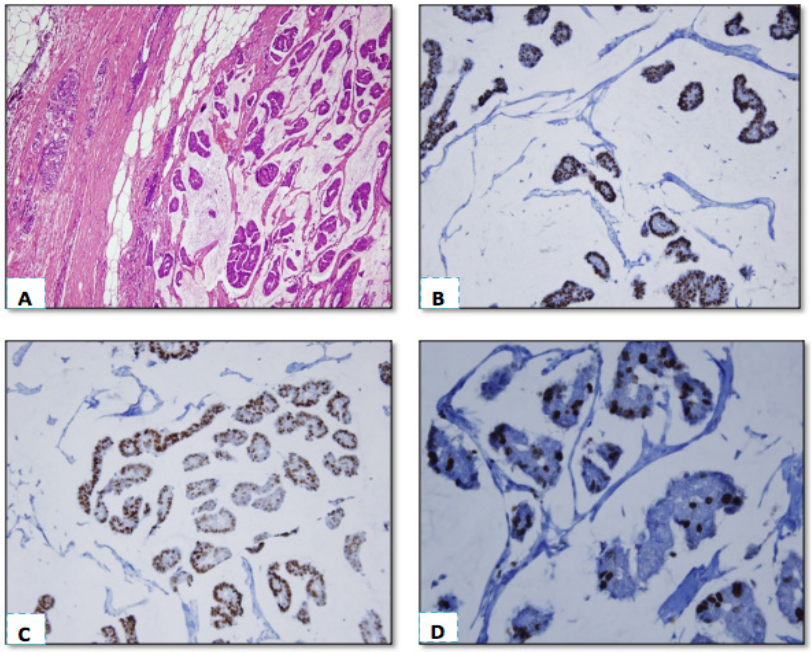

Figure 1. A. Neoplastic cells form papillary and glandular structures within extracellular mucin pools (Hematoxylin and eosin x10), **B.** Diffuse and strong intranuclear immunoreaction for estrogen receptor antibody in a case of mucinous carcinoma of the breast [Diaminobenzydin (DAB)-anti estrogen receptor-Mayer's hematoxylin x20], **C.** Moderately intense nuclear expression of progesterone receptor in nearly three quarters of neoplastic cellular nuclei (DAB-anti progesterone receptor-Mayer's hematoxylin x20), **D.** Low proliferative rate, as shown by anti-Ki67 labelling of neoplastic cells (DAB-anti Ki 67-Mayer's hematoxylin x40)

The pathological tumor stage was assessed according to the American Joint Committee on Cancer's 7th Staging System. PMBC was defined as having a mucinous component more than 90% and specialized pathologists with extensive experience in breast pathology performed a pathologic slide review. As recently revised (5, 6), the intrinsic subtypes of the tumor were defined as follows: luminal A, ER(+) or PR(+), human epidermal growth factor receptor 2 (HER2)-neu (-), Ki67 20%; luminal B, ER(+) or PR(-/+), HER2-neu (-/+), Ki67 >20%; HER2-enriched, ER(-) PR(-) HER2-neu (+); triple-negative, ER(-) PR(-).

Statistical Analysis

For statistical analysis, the Statistical Package for the Social Sciences (SPSS), version 25.0, was used (IBM Corp., Armonk, NY, USA). The data obtained from each continuous variable were analyzed using various descriptive, graphical, and statistical methods to determine whether or not they were normally distributed. In addition to descriptive statistical methods (number, percentage, mean, median, standard deviation, etc.), quantitative data was compared using the independent sample t-test. For qualitative comparisons between groups, the chi-square test (Pearson chi-square, continuity correction, Fisher's Exact test) was used. The significance of the results was determined using a 95% confidence interval.

Results

Patients and Tumors Characteristics

The patients were all female, with a median (range) age of 63 (28–90) years. The median tumor size was 23 (5–100) mm. Out of 87 patients, 60 (69%) had breast-conserving surgery (BCS), while 27 (31%) had mastectomy (Table 1). Only 15 of the patients with axillary staging had lymph node metastasis, 11 of which were N1 and four of which were N2.

As can be seen in Table 1, 58 patients (66.7%) had SLNB, and 24 had axillary dissection due to positive SLNB or positive clinical axilla. Only two of the 15 patients who had a positive SLNB and underwent axillary dissection had non-sentinel positivity. Due to age and comorbidities, five patients were not suitable for axillary surgery.

From all the tumors that were included in this study, 11 (12.6%) had lympho-vascular invasion (LVI), whereas 37 tumors (42.5%) were HG 1, 45 tumors (51.7%) were HG 2, and only 5 tumors (5.7%) were HG 3. Necrosis was seen in only six (6.9%) of the patients. Almost all patients were in the luminal group (95.4%).

Only five patients (5.7%) had HER2-neu positive tumors, while 83 tumors (95.4%) were ER-positive and 77 tumors (88.5%) were PR-positive. The majority of patients with Ki67 index (n = 56) had a Ki67 score less than 20% (71.4%).

Adjuvant Systemic Therapy

Adjuvant chemotherapy was given to only 23 patients (26.4%). With the exception of four patients, all patients had hormone therapy since their tumors were ER negative.

Outcome Analysis

The median follow-up time was 53 (6–207) months. None of the patients had a local or systemic recurrence. Only 10 out of 87 patients (11.5%) died during the follow-up and treatment period due to non-cancer causes.

As shown in Table 2, in this study we found that tumor diameter and LVI were statistically significantly higher in grade II/III tumors (p = 0.039 and p = 0.021, respectively). Also, we found that necrosis was only seen in grade II/III tumors (p = 0.036). Additionally, tumor diameter was larger (p = 0.027) and lymph node metastasis was more likely (p = 0.013) in patients younger than 50 years. Moreover, HER2 positivity was statistically significantly more common in patients younger than 50 years (p = 0.026). In a similar way, Ki67 less than 20% was statistically significant in grade I tumors and in patients older than 50 (p = 0.006 and p = 0.033, respectively). Furthermore, patients who had not received chemo/radiotherapy were older than 50 years (p = 0.002).

Radiological Investigation Results

Our radiological investigations were the same as reported in previous studies. Mammographically, PMBC tends to present as a well-circumscribed lesion (7-9), which is echogenic to the breast fat on ultrasonography (10). Thus, a significant number of lesions could be misinterpreted as benign on screening mammograms (10, 11).

Interestingly, a delay in the diagnosis may not cause a significant adverse outcome for most women (2). On magnetic resonance imaging, PMBC is associated with a very specific appearance, showing a gradually enhancing contrast pattern with rim or heterogeneous enhancement and a very high signal intensity on T2-weighted images (12, 13), as we show in Figure 2.

Discussion and Conclusion

Mucinous carcinoma is a rare type of cancer that can arise in mucin-producing epithelial tissues. MBC is rarely seen in clinical practice, comprising approximately 2% of all invasive breast cancers (1). In the literature, Di Saverio et al. (14) and Vo et al. (15) presented multivariate analysis results. These studies indicate that independent factors such as age, tumor size, lymph node status, and ER status are associated with a particularly good prognosis in MBC patients. PMBC is a cancer of older women, with only 1% of PMBC patients being under the age of 35 years (2, 16). The median age of the patients included in this study was 63, which is similar to a study done by Zhou et al. (17).

Previous studies have shown that sentinel lymph node metastasis is the most important prognostic factor for disease-free survival (1, 18, 19). In this study, a small number of patients (15/87) had lymph node metastasis, and a favorable prognosis was noted for patients who had no metastasis to lymph nodes. Compared to the other studies, nodal positivity was detected in 17.2% of our study patients whereas in other series, this percentage ranged from 2% to 20% (17-20). Only two of the 15 patients (2/15; 13.3%) who had a positive SLNB and underwent axillary dissection had non-sentinel positivity. According to the findings of the ACOSOG Z0011 study, axillary curettage would be unnecessary for patients with sentinel lymph node positivity in the pure mucinous carcinoma patient group (21).

We found that tumor diameter in PMBC was significantly larger in grade II/III tumors and in patients under the age of 50, which was consistent with the findings of Tahmasebi et al. (22). In a group of 111 patients with MBC, Diab et al. (23) observed a correlation between the size of the primary tumors and the status of the lymph nodes. When the tumor size was less than 2 cm, metastasis to lymph nodes was not indicated in 90% of the patients, which is in agreement with our study results of 83%. Another study by Skotnicki et al. compared the clinical characteristics and treatment results of 70 patients with PMBC and 40 patients with MMBC, treated at a single institution for 25 years.

Table 1. Patients and tumors characteristics (n = 87)

Characteristic	Category	n	%	Median (range)
Age (years)	All	87	100.0	63 (28–90)
Age group	<50 years	26	29.9	
	≥50 years	61	70.1	
pT stage	pT1	36	41.4	
	pT2	44	50.6	
	pT3	7	8.0	
pN stage	pN0	72	82.8	
	pN1	11	12.6	
	pN2	4	4.6	
Tumor diameter (mm)	All	87	100.0	23 (5–100)
Breast surgery	BCS	60	69.0	
	Mastectomy	27	31.0	
	Not done	5	5.7	
Axillary surgery	SLNB	58	66.7	
	ALND	24	27.6	
Grade	I	37	42.5	
	II	45	51.7	
	III	5	5.7	
LVI	Positive	11	12.6	
	Negative	76	87.4	
Necrosis	Positive	6	6.9	
	Negative	81	93.1	
ER	Positive	83	95.4	
	Negative	4	4.6	
PR	Positive	77	88.5	
	Negative	10	11.5	
HER2	Positive	5	5.7	
	Negative	82	94.3	
Ki-67 (n=56)	<20%	40	71.4	10 (2–50)
	≥20%	16	28.6	
Molecular subtype	Luminal	83	95.4	
	Non- Luminal	4	4.6	
Adjuvant therapy	None*	14	16.1	
	RT	50	57.5	
	CT+RT	23	26.4	
Follow-up time (months)	All	87	100.0	53 (6–207)
Relapse	Yes	0	0.0	
	No	87	100.0	
Mortality	Yes**	10	11.5	
	No	77	88.5	

ER: estrogen receptor; PR: progesterone receptor; CT: chemotherapy; RT: radiotherapy; LVI: lymph vascular invasion; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; ALND: axillary lymph node dissection; *: they received only hormone therapy, **: all deaths were due to non-cancer causes

Table 2. Patient characteristics according to grade and age (n = 87)

		Grade			Age		
		I (n = 37)	II/III (n = 50)		<50 (n = 26)	≥50 (n = 61)	
Characteristic	**Category**	**n (%)**	**n (%)**	***p***	**n (%)**	**n (%)**	***p***
Age#	All	61.22±13.38	59.42±16.48	0.588[a]	41.08±6.76	68.33±9.26	-
Age group	<50	9 (34.6)	17 (65.4)	0.461[c]	-	-	
	≥50	28 (45.9)	33 (54.1)		-	-	
pT stage	pT1	19 (52.8)	17 (47.2)	0.160[c]	10 (27.8)	26 (72.2)	0.902[c]
	pT2/3	18 (35.3)	33 (64.7)		16 (31.4)	35 (68.6)	
pN stage	pN0	31 (43.1)	41 (56.9)	0.999[c]	17 (23.6)	55 (76.4)	**0.013[c]***
	pN1/2	6 (40.0)	9 (60.0)		9 (60.0)	6 (40.0)	
Tumor diameter (mm)#	All	23.32±15.33	30.98±17.83	**0.039[a]***	33.92±18.72	25.08±15.87	**0.027[a]***
Breast surgery	BCS	26 (43.3)	34 (56.7)	0.999[c]	18 (30.0)	42 (70.0)	
	Mastectomy	11 (40.7)	16 (59.3)		8 (29.6)	19 (70.4)	
Axillary surgery	Not done	2 (40.0)	3 (60.0)	0.98[db]	0 (0.0)	5 (100.0)	0.246[b]
	SLNB	25 (43.1)	33 (56.9)		17 (29.3)	41 (70.7)	
	ALND	10 (41.7)	14 (58.3)		9 (37.5)	15 (62.5)	
Grade	I	-	-		9 (24.3)	28 (75.7)	0.461[c]
	II/III	-	-		17 (34.0)	33 (66.0)	
LVI	Positive	1 (9.1)	10 (90.9)	**0.021[d]***	5 (45.5)	6 (54.5)	0.393[c]
	Negative	36 (47.4)	40 (52.6)		21 (27.6)	55 (72.4)	
Necrosis	Positive	0 (0.0)	6 (100.0)	0.036[d]*	2 (33.3)	4 (66.7)	0.999d
	Negative	37 (45.7)	44 (54.3)		24 (29.6)	57 (70.4)	
ER	Positive	36 (43.4)	47 (56.6)	0.633[d]	24 (28.9)	59 (71.1)	0.580[d]
	Negative	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)	
PR	Positive	34 (44.2)	43 (55.8)	0.507[d]	23 (29.9)	54 (70.1)	0.999[d]
	Negative	3 (30.0)	7 (70.0)		3 (30.0)	7 (70.0)	
HER2	Positive	0 (0.0)	5 (100.0)	0.069[d]	4 (80.0)	1 (20.0)	**0.026[d]***
	Negative	37 (45.1)	45 (54.9)		22 (26.8)	60 (73.2)	
Ki-67(n = 56)	<20%	22 (55.0)	18 (45.0)	**0.006[d]***	9 (22.5)	31 (77.5)	**0.033[c]***
	≥20%	2 (12.5)	14 (87.5)		9 (56.3)	7 (43.7)	
Molecular subtype	Luminal	36 (43.4)	47 (56.6)	0.633[d]	24 (28.9)	59 (71.1)	0.580[d]
	Non-Luminal	1 (25.0)	3 (75.0)		2 (50.0)	2 (50.0)	
Adjuvant therapy	Didn't receive	6 (42.9)	8 (57.1)	0.052[b]	1 (7.1)	13 (92.9)	**0.002[b]***
	RT	26 (52.0)	24 (48.0)		12 (24.0)	38 (76.0)	
	CT+RT	5 (21.7)	18 (78.3)		13 (56.5)	10 (43.5)	
Mortality	Yes	3 (30.0)	7 (70.0)	0.507[d]	2 (20.0)	8 (80.0)	0.716[d]
	No	34 (44.2)	43 (55.8)		24 (31.2)	53 (68.8)	

*: p<0.05, #: Mean ± Standard deviation; [a(t)]: independent sample t-test; x^2: chi-square tests ([b]: pearson chi-square, [c]: continuity correction, [d]: fisher's exact test)

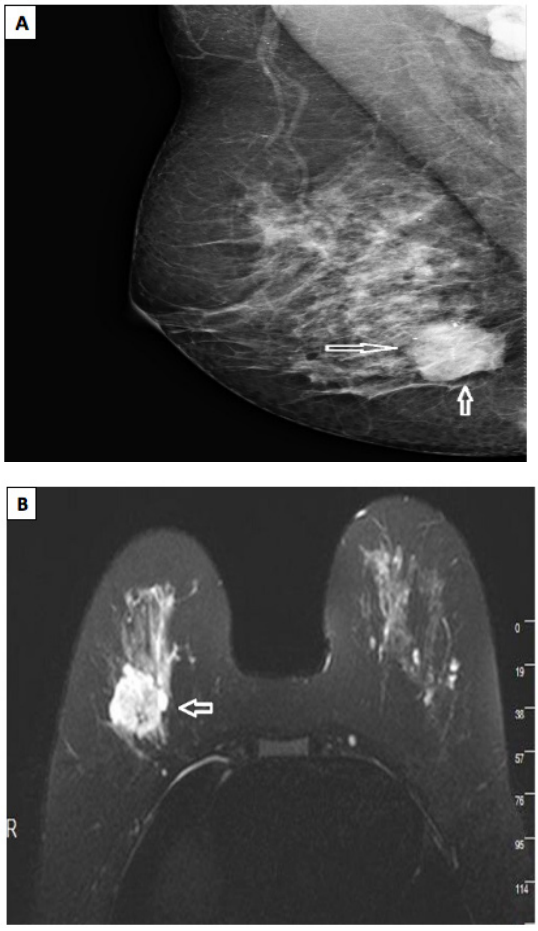

Figure 2. A. Mucinous breast carcinoma mammography, **B.** Magnetic resonance imaging

*Images had taken from our diagnosed patients

Their results demonstrated that the only difference between PMBC and MMBC was nodal status, as MMBC showed a significantly higher incidence of axillary nodal metastasis compared to PMBC (25% *versus* 10%) (17).

Furthermore, a recent study found that PMBC and MMBC were clinicopathologically distinct in terms of gross findings and lymph node status. The average length of follow-up was 24.5 months. MMBCs were highly proliferative, with more complications compared to PMBC. Lymph node involvement is the most important prognostic factor, and it is independent of other prognostic factors, such as tumor size, patient age, and hormonal receptor status (24). According to our findings, lymph node involvement, mean tumor diameter, high Ki67 expression, and HER2 positivity were all significantly increased in the group under 50 years old. These findings are consistent with the earlier reports of young-age aggressive tumor structure. However, no local, regional, or systemic recurrence was found in this study. This could be explained by the distinctive structure of mucinous carcinomas.

The PMBC data shows a high percentage of hormone receptor expression. These findings are consistent with Saverio's findings from large data, which reported a rate of positivity of 94% for ER and 81% for PR (14). A high rate of hormone receptor expression and old age were associated with a favorable prognosis in patients. Patients over the age of 50 did not receive chemo/radiotherapy, which explains their high sensitivity to hormone therapy and lack of lymph node metastasis.

Compared to other breast carcinoma forms, mucinous carcinoma has less genetic instability (25). Several studies have shown that PMBC has clinicopathological heterogeneity (26), but 95.4% of patients in this study were in the luminal subgroups. We couldn't classify luminal subgroups because we didn't have the values for Ki67 expression for all patients. Moreover, it is genetically heterogeneous and lacks any sort of pathognomonic genetic alterations (26, 27). Further clinical trials with larger sample sizes, as well as molecular and genetic studies, need to be conducted to get a better understanding of the molecular biology and clinical outcomes of PMBC.

In conclusion, MBC is a rare type of breast cancer with a favorable prognosis. Patients with MBC have a low rate of lymph node metastasis and almost all patients are in the luminal subgroups. PMBC has a lower incidence, smaller tumor size, benign lesion-like characteristics, low axillary lymph node metastasis, low grade, low recurrence rate, and a higher survival rate. We believe that minimal axillary surgery would be the most appropriate approach during patient treatment due to the low rate of lymph node involvement and favorable prognosis in PMBC patients.

Acknowledgement

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Ethics Committee Approval: This study was based on an analysis of a large mono-institutional series of breast cancer patients treated in a high-volume reference center with widely standardized treatment and management.

Informed Consent: Retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: S.E., N.C., E.O.; Design: S.E., S.K., N.C., E.O., M.M.; Data Collection and/or Processing: S.E., M.T., S.O., M.M.; Analysis and/ or Interpretation: S.E., M.T., S.K., H.K., S.O., V.O., N.C., E.O., R.Y., M.M.; Literature Searching: S.E.; Writing: S.E., M.T., S.K.

Conflict of Interest: No conflict of interest was declared by the authors.

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