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Skin manifestations in sulfur mustard exposed victims with ophthalmologic complications: Association between early and late phase

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ABSTRACT

Context: Sulfur mustard (SM) was used during the Iraq-Iran war (1980–1988). Exposed veterans continue to suffer from its ocular, skin, and respiratory complications.
Objective: We aimed to evaluate associations between early (at the time of acute exposure) and decades later skin manifestations in individuals with severe ophthalmologic complications secondary to sulfur mustard exposure.
Materials and methods: One hundred forty-nine veterans with severe ocular injuries were evaluated for acute and chronic skin complications. Logistic regression models were used to examine the associations between early and late skin manifestations.
Results: Late skin complaints were observed in nearly all survivors who had early skin lesions (131 out of 137; 95.62%). Seven out of 12 patients (58.33%) who did not have early skin lesions ultimately developed late skin complications. There was a significant relationship between the presence of lesions at the time of exposure and developing late skin complaints (two-sided Fisher's exact test, OR = 15.59, $p < 0.001$). There was an association between having at least one early skin lesion and occurrence of late skin complications. Survivors with blisters at the time of chemical exposure were more likely to complain of itching (95% CI: 3.63–25.97, $p < 0.001$), burning (OR = 11.16; 95% CI: 2.97–41.89, $p < 0.001$), pigmentation changes (OR = 10.17; 95% CI: 2.54–40.75, $p = 0.001$), dryness (OR = 6.71, 95% CI: 1.22–37.01, $p = 0.03$) or cherry angioma (OR = 2.59; 95% CI:1.21–5.55, $p = 0.01$) during the late phase. Using multivariate logistic models, early blisters remained significantly associated with latent skin complaints. Of note, the genitalia and great flexure areas were the most involved anatomical sites for both early and late skin lesions in SM exposed survivors.
Conclusion: According to this study, the presence of blisters at the time of exposure to SM is the most important predictor of developing dermatologic complications decades later in patients with severe ophthalmologic complications from sulfur mustard exposure.

1. Introduction

Chemical warfare agents were first widely used in World War I and were employed again during the Iraq-Iran war (1980–1988). About 45,000 victims are still suffering from long-term complications of SM exposure during the Iran-Iraq War [12]. Unprotected victims who were exposed to either vapor or liquid forms of the sulfur mustard have been documented as developing deforming skin blisters in addition to respiratory and ophthalmologic damage. The skin in particularis significantly affected by exposure to sulfur mustard, because of its large surface area and the sensitivity of basal keratinocytes [20,21,26].

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About 80% of the SM that contacts human skin will evaporate and only the remaining 20% will penetrate into the underlying tissue. However, once absorbed by the skin, SM cannot be removed and within ten minutes bound to the epidermal and dermal tissue, mostly in the cornified layer. Sulfur mustard damages the cells that regenerate after injury, such as basal cells in the skin [15].

Sulfur mustard forms carbonium ions and transient complexes with large molecules that induce severe electrophilic tissue reactions. SM is also mutagenic and cytotoxic via modifications in DNA structure. Through these mechanisms, sulfur mustard affects nearly every organ system, including the dermatological, ophthalmological, respiratory, haematological, gastrointestinal, endocrine, neuro-muscular, and immune systems. The pathophysiology of dermatological injury has been studied to a limited extent. Histopathological examination of skin biopsies has revealed epidermal atrophy, keratosis, basal membrane hyperpigmentation, fibrosis, and melanophages within the dermis [3,4].This is thought to occur because SM reacts with skin proteins, suppressing laminin and integrin and leading to loss of cellular and extracellular structure. These skin proteins constitute the attachment protein complex responsible for epidermal-dermal adhesion [23]. Separation of the epidermal cells causes early phase symptoms like erythema and blistering [3].

Severe inflammation secondary to SM-related tissue damage also causes damage to other components of the skin, including sweat and sebaceous glands and pigment cells [5]. Despite knowledge about the acute effects of sulfur mustard injury, there is incomplete information regarding the cellular and molecular mechanisms responsible for the chronic adverse effects of exposure [1].

Studies about chronic skin effects in chemical-injured veterans are limited [3,7]. Most victims experience non-lethal but debilitating injuries with long-term morbidity. Moreover, there are no effective therapeutic options for the delayed toxic effects of SM. It is thus important to understand how chronic complications and subsequent skin cancers can be decreased via close management and follow-up of acute effects [20,14,22]. In the present study, we aimed to find the spatial and temporal relationships between early and late skin lesion in SM-exposed survivors with severe ophthalmologic complications.

2. Methods

This cross-sectional study was performed to assess the acute and chronic skin complications and the relationship between them in Iranian SM exposed survivors with severe ocular injuries. A total of 149 SM-exposed Iranian victims suffering from severe ocular injuries were recruited for the study. Severity of ocular injuries was verified by the Medical Commission of Veterans and Martyrs Affairs Foundation (VMAF) of Iran. Written informed consent was obtained from all subjects. Demographic characteristics, including sex, age, age at the time of exposure, time since first exposure, and frequency of exposure were obtained from patient medical records. Data on acute and sub-acute skin manifestations, including erythema, blister, scaling, and pigmentation were also collected from patient records. Chronic dermatologic disease was assessed using patient-reported symptoms and physical exam findings observed by an expert dermatologist (cherry angioma, burning, pigmentation changes, xerosis, photosensitivity, hives, hair loss, and pruritis).

The locations of lesions were classified based on location: head & neck, trunk, mucous membranes, flexures, genitalia, extremities, or generalized. Univariate and multivariate logistic regression models were used to examine whether there were relationships between early and late skin complaints in SM exposed survivors. All statistical analysis was performed using statistical software SPSS 16.0.

Table 1
Demographic characteristics of SM exposed survivors with severe ophthalmologic complications (n = 149).

Sex No. (%)	
Male	148 (99.33%)
Age, years	
Mean (SD)	45.84 (8.64)
Median (Range)	43 (22–76)
Time since first exposure, years	
Mean (SD)	21.9 (1.14)
Median (Range)	22 (16–26)
Age at the time of exposure, years	
Mean (SD)	23.93 (8.40)
Median (Range)	21.50 (1–53)
Frequency of chemical gas exposure, no. (%)	
One exposure	99 (66.44%)
More than one exposure	50 (33.56%)

3. Results

The patient characteristics are shown in Table 1. Of the 149 victims with SM exposure-induced severe ophthalmological injuries, 137 (91.94%) cases had at least one type of skin lesion at the time of SM exposure. The most common type of cutaneous findings were erythema (78.52%), blistering (71.81%), scaling (85.23%), and pigmentation (86.58%) (Table 2). The distribution of skin lesions at the time of exposure is shown in Table 2. Of note, the genitalia and great flexures are the most commonly involved anatomical sites (56.41%), followed by the head and neck region (Table 2).

Of the 149 chemical warfare victims, 92.62% had late cutaneous complaints. The most common skin problems were as follows: itching (83.89%), burning (72.48%), cherry angioma (71.81%), pigmentation changes (61.74%), dryness (38.25%), photosensitivity (14.76%), hair loss (2.68%), and hives (1.34%). The location distribution of late skin lesions is shown in Table 3. Burning, pruritis, and pigmentation changes were most found in the great flexures and genitalia. The trunk was the most common site for cherry angioma and the mucous membranes for xerosis.

Late skin complaints were observed nearly in all survivors with early skin lesions 95.62% (131 out of 137). Seven out of 12 patients without skin lesions (58.33%) at the time of exposure also developed late skin complaints. There was a significant relationship between lesions at the time of chemical exposure and developing late skin complaints (two-sided Fisher's exact test, OR = 15.59, $p < 0.001$). Univariate logistic regression predicting late skin complaints in chemical warfare victims is illustrated in Tables 4–6 .

Univariate logistic regression indicated that patients with blisters at the time of exposure were 9.71 times more likely to develop itching complaint later (95% CI: 3.63–25.97, $p < 0.001$). Also, patients with early erythema, scaling, and pigmentation lesions were significantly more likely to have pruritis later (Table 4). The univariate analysis also showed that having latent burning was associated with having blisters (OR = 9.97, 95% CI: 4.35–22.81, $p < 0.001$), erythema (OR = 6.31, 95% CI: 2.71–14.68, $p < 0.001$), scaling (OR = 3.23; 95% CI:1.27–8.20, $p = 0.02$) and being 20 years old or younger (OR = 2.35; 95% CI:1.07–5.17, $p = 0.03$) at the time of chemical exposure (Table 4).

Having blister, erythema and being 20 years old or younger at the time of chemical exposure was significantly related to developing cherry angioma (Table 5).

Early cutaneous lesions (blister, scaling, pigmentation and erythema) were not significantly related to developing late photosensitivity (Table 6). The victims with blister and erythema lesions at the time of chemical exposure were significantly at higher risk

Table 2
Frequency distribution of skin lesions at the time of SM exposure according to the location of lesions.

	Erythema No. (%)	Blisters No. (%)	Scaling No. (%)	Pigmentation No. (%)
Total	117 (78.52%)	107 (71.81%)	127 (85.23%)	129 (86.58%)
Location of Lesions				
Head & Neck	21 (17.95%)	21 (19.63%)	21 (16.53%)	20 (15.50%)
Trunk	9 (7.69%)	8 (7.48%)	7 (5.51%)	8 (6.20%)
Extremities	15 (12.82%)	14 (13.08%)	13 (10.24%)	12 (9.30%)
Great Flexures	66 (56.41%)	57 (53.27%)	48 (37.79%)	45 (34.88%)
Genitalia	66 (56.41%)	58 (54.21%)	49 (38.58%)	46 (35.66%)
Mucous Membranes	–	–	–	1 (0.77%)
Generalized	39 (33.33%)	38 (35.51%)	68 (53.54%)	72 (55.81%)

Table 3
Frequency of distribution of SM late skin complaints according to the location of lesions.

	Burning No. (%)	Pruritis No. (%)	Cherry angiomata No. (%)	Pigmentation changes No. (%)	Xerosis No. (%)	Photo sensitivity No. (%)	Hairloss No. (%)	Hives No. (%)	Bulla No. (%)
Total	108 (72.48)	125 (83.89)	107 (71.81)	92 (61.74)	57 (38.25)	22 (14.76)	4 (2.68)	2 (1.34)	–
Location of lesions									
Head & Neck	8 (7.41)	12 (9.60)	1 (0.93)	12 (13.04)	2 (3.51)	22 (100)	3	1	–
Trunk	11 (10.18)	16 (12.80)	96 (89.72)	23 (25.00)	–	–	–	1	–
Extremities	18 (16.67)	24 (19.20)	17 (15.89)	42 (45.65)	–	–	–	–	–
Great Flexures	34 (31.48)	46 (36.80)	1 (0.93)	52 (56.52)	2 (3.51)	–	–	–	–
Genitalia	28 (25.93)	40 (32.00)	1 (0.93)	56 (60.87)	2 (3.51)	–	–	1	–
MucousMembranes	–	–	–	–	26 (45.61)	–	–	–	–
Generalized	22 (20.37)	26 (20.80)	1 (0.93)	12 (13.04)	25 (43.86)	–	1	–	–

Table 4
Univariate logistic regression predicting pruritis and burning in SM exposed survivors.

	With risk factor		Without risk factor				
Prevalence of pruritis RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	100	93.46	25	59.52	<0.001	9.71	(3.63–25.97)
Erythema	106	90.60	19	59.37	<0.001	6.59	(2.58–16.87)
Scaling	112	88.19	13	59.09	0.002	5.17	(1.89–14.14)
Pigmentation	112	86.82	13	65.00	0.02	3.55	(1.24–10.15)
Chemical exposure ≥ 1 time	41	82.00	84	84.85	0.81	0.81	(0.33–2.01)
Age ≤ 20 at the time of exposure	52	85.24	73	83.00	0.71	1.19	(0.48–2.92)
At least one type of early skin lesion	120	87.59	5	41.66	0.001	9.88	(2.82–34.67)
Prevalence of burning RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	92	86.00	16	38.09	<0.001	9.97	(4.35–22.81)
Erythema	95	81.20	13	40.62	<0.001	6.31	(2.71–14.68)
Scaling	97	76.40	11	50.00	0.02	3.23	(1.27–8.20)
Pigmentation	97	75.19	11	55.00	0.06	2.48	(0.94–6.52)
Chemical exposure ≥ 1 time	36	72.00	72	72.73	0.92	0.96	(0.45–2.06)
Age ≤ 20 at the time of exposure	50	82.00	58	65.91	0.03	2.35	(1.07–5.17)
At least one type of early skin lesion	104	75.91	4	33.33	0.004	6.30	(1.78–22.28)

of having late pigmentation changes complaint (OR = 8.78, 95% CI: 3.88–19.88, p < 0.001 and OR = 6.24, 95% CI: 2.62–14.86, p < 0.001, respectively). Table 5 shows the results of univariate regression analysis in more details.

Blisters remained a significant predictor for developing latent pruritis after adjusting the early skin lesions for each other. Chemical warfare victims with early blister lesions were 8.24 times more likely to develop late phase pruritis (OR = 8.24, 95% CI: (1.97–34.50), p = 0.004), and 6.71 times more likely to have xerosis (OR = 6.71, 95% CI: 1.22- 37.01, p = 0.03). In addition, multivariate logistic analysis indicated that patients with early blistering were at higher risk of developing burning (OR = 11.16; 95% CI: 2.97–41.89, p < 0.001) and pigmentation changes (OR = 10.17, 95% CI: 2.54–40.75, p = 0.001).

Table 5
Univariate logistic regression predicting cherry angiomata and pigmentation changes in SM exposed survivors.

	With risk factor		Without risk factor				
Prevalence of cherry angioma							
RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	83	77.57	24	57.14	0.01	2.59	(1.21–5.55)
Erythema	89	76.07	18	56.25	0.03	2.47	(1.09–5.60)
Scaling	95	74.80	12	54.54	0.051	2.47	(0.98–6.27)
Pigmentation	96	74.42	11	55.00	0.07	2.38	(0.91–6.25)
Chemical exposure ≥ 1 time	36	72.00	71	71.71	0.97	1.01	(0.48–2.16)
Age ≤ 20 at the time of exposure	51	83.61	56	63.67	0.01	2.91	(1.30–6.52)
At least one type of early skin lesion	104	75.91	3	25.00	0.001	9.45	(2.42–36.99)
Prevalence of pigmentation changes							
RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	81	75.70	11	26.19	<0.001	8.78	(3.88–19.88)
Erythema	83	70.94	9	28.12	<0.001	6.24	(2.62–14.86)
Scaling	81	63.78	11	50.00	0.22	1.76	(0.71–4.38)
Pigmentation	82	63.56	10	50.00	0.24	1.74	(0.68–4.50)
Chemical exposure ≥ 1 time	26	52.00	66	66.67	0.08	0.54	(0.27–1.08)
Age ≤ 20 at the time of exposure	41	67.21	51	57.95	0.25	1.49	(0.75–2.94)
At least one type of early skin lesion	88	64.23	4	33.33	0.06	3.59	(1.03–12.54)

Table 6
Univariate logistic regression predicting xerosis and photosensitivity and in SM exposed survivors.

	With risk factor		Without risk factor				
Prevalence of xerosis							
RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	50	46.73	7	16.67	0.001	4.39	(1.79–10.74)
Erythema	51	43.59	6	18.75	0.01	3.35	(1.28–8.74)
Scaling	48	37.79	9	40.91	0.78	0.88	(0.35–2.21)
Pigmentation	49	38.00	8	40.00	0.86	0.92	(0.35–2.41)
Chemical exposure ≥ 1 time	16	32.00	41	41.41	0.26	0.67	(0.32–1.36)
Age ≤ 20 at the time of exposure	21	34.43	36	40.91	0.42	0.76	(0.38–1.49)
At least one type of early skin lesion	55	40.14	2	16.67	0.13	3.35	(0.71–15.90)
Prevalence of Photosensitivity							
RISK FACTOR	N	%	N	%	P	OR	95% CI
Acute dermatologic complication							
Blistering	19	17.76	3	7.14	0.10	2.81	(0.78–10.04)
Erythema	20	17.09	2	6.25	0.16	3.09	(0.68–14.00)
Scaling	21	16.53	1	4.54	0.20	4.16	(0.53–32.64)
Pigmentation	21	16.28	1	5.00	0.31	3.69	(0.47–29.12)
Chemical exposure ≥ 1 time	7	14.00	15	15.15	0.85	0.91	(0.35–2.40)
Age ≤ 20 at the time of exposure	9	14.75	13	14.77	0.99	1.00	(0.40–2.51)
At least one type of early skin lesion	21	15.33	1	8.33	0.69	1.99	(0.24–16.25)

4. Discussion

Our study showed that nearly all (91.94%) patients with SM exposure-induced severe ophthalmological injuries had at least one of the acute phase cutaneous lesions, especially in the genitalia and great flexures. According to the literature, the severity of acute skin problems depends on the primary location (more commonly in warm and humid skin regions), dosage, and intensity and duration of exposure [20,26]. As the depth of dermatological damage increases (e.g. causing blistering and necrotic wounds), the area and severity as well as the risk of late complications increase [3]. Factors such as exposure time, concentrations of mustard gas, and protective equipment (masks and specialized gas troops cloth uniform) are associated with the risk of acute lesions [19,3,7]. Patients with lower age, white race, and female gender experience a severe form of acute manifestation. Some specific anatomical areas such as scrotum, groin, armpits and genitalia with less evaporation rate, secondary to warmth and humidity, and areas of the body under tight clothing (e.g. military belt), secondary to the epidermis tightening and flaccidity are the most common sites of acute involvement [3].

Excessive dry skin (xerosis), hyperpigmentation, burning sensation, pruritis, hypopigmentation, and cherry angioma are the most common non-specific skin lesions reported in the literature [4,6,17]. The previously reported differences in the incidence and prevalence of these lesions are affected by factors such as age,

socioeconomic status, geography, occupation, and genetics [8]. The differences were also attributed to variations in patient sampling and assessment methods as well as the dose, duration, and extension of exposure [10]. Effects of exposure to different amount of SM showed that concentrations of 100–400 mg/min/m^3 causes slight skin effects, while severe skin damage occurs with doses exceeding 750–1000 mg/min/m^3 [3]

Our data showed that nearly all patients (92.62%) developed late cutaneous complications. This rate is much higher than that reported by Emadi et al. (24.5%) [7]. We found that patients having at least one of the early skin lesions were at a higher risk of reporting late skin lesions, especially pruritis, cherry angioma, and burning. The occurrence and persistence of these skin lesions are directly dependent on the duration and the severity of exposure [3].

The high prevalence of developing severe acute and subsequent chronic skin lesions in our study population compared to previous studies may therefore be due to exposure to higher doses or longer durations of SM exposure.

The most common chronic dermatologic complaint was itching and was frequently associated with dryness and burning. Although, increased TEWL (trans-epidermal water loss) and decreased sebum production have been postulated in the pathogenesis of skin xerosis and pruritis, the exact mechanism of pruritis is unknown [17]. Though pruritis worsens in dry weather and after physical activity, the role of psychological factors should not be ignored [3,10]. The psychological effects and sleep impairment due to pruritis can severely affect quality of life [20]. Of note, a previous study reported dry skin in the extremities [4], whereas our study observed dry skin most commonly in the mucous membranes.

We found that, in general, the prevalence of chronic skin complaints was associated most strongly with the early presence of blistering and erythema. These two acute lesions should therefore be considered to be risk factors for developing chronic complications. Patients with early scaling lesions were at higher risk of reporting pruritis and burning. Patients with pigmentation lesions at the time of chemical exposure were more likely to have late pruritis. Each of early cutaneous lesions (blister, scaling, pigmentation, and erythema) was not significantly related to developing late photosensitivity. In our study, we concluded that blistering (the most severe acute phase symptom), was a significant predictor for developing late phase pruritis.

Hyperpigmentation was also noted as a long-term complication of SM exposure in this study. Possible mechanisms of hyperpigmentation in the study population other than chronic inflammation, pruritis, and excoriation include higher melanin content, activated melanocytes, pigmentary incontinence due to hydropic changes in epidermal basal layer, increase in tyrosinase activity due to depletion of glutathione, increased melanogenesis and up-regulation of Melanocyte Stimulating Hormone (MSH) centrally from hypothalamus by interleukin-1 and tumor necrosis factor-α. Interestingly, hypopigmentation has also been reported in the SM-exposed population via a proposed mechanism of melanocyte destruction secondary to high concentration SM exposure. Given the reports of a higher prevalence of vitiligo in SM-exposed patients, the mechanism of SM-mediated changes in pigmentation remains in doubt [10]. Future studies will help us better understand which mechanism is more important in SM exposure.

In this study, we found that patients aged 20 years or less at the time of chemical exposure were at higher risk of developing cherry angiomata and burning in comparison with older subjects (Tables 4 and 5). Prior studies have shown that the acute onset of skin lesions in children and adolescents compared to adults is shorter and their lesions are more severe. This can be explained by the increased skin sensitivity and greater vulnerability of this population. Of note, lesions of the genitalia have been less frequently reported in children than in adults [18].

We found that both the genitalia and great flexure areas, followed by the head & neck, extremities, and trunk were the most commonly involved anatomical sites for skin lesions at the time of SM exposure. Our results show that burning, pruritis, and pigmentation changes were most commonly found in the great flexures and genitalia, whereas the trunk and extremities were the most common sites for cherry angiomata. Photosensitivity was most commonly observed on the head and neck.

The higher prevalence of cherry angiomata (ranged between 36 and 71.81%) with larger size and diffuse dissemination were reported in the survivors. Although the exact mechanism is not clear, direct SM-mediated DNA damage and release of angiogenic cytokines has been proposed [10]. A few studies have reported higher prevalences of disorders like cherry angioma, alopecia areata, lichen planus, psoriasis, dermatitis seborrheic, vitiligo, and discoid lupus erythematosus, tinea versicolor, and chronic urticaria in subjects exposed to SM compared with the general population. Complete alopecia was reported in one patient. It seems, however, that there is not enough evidence yet to make definitive claims about the increased prevalence of these conditions [5,17,8]. Interestingly, dry skin and associated itching appears to intensify gradually over time in SM-exposed patients, while other skin complications decrease [4]. A possible mechanism for the increase in skin pathology in this population could be SM-mediated immune dysregulation [3]. Both humoral and cellular immune functions are impaired after SM exposure [3]. Changes in pro-inflammatory markers and cytokines (such as IL-1 beta, IL-8, TNF-alpha, and IL-6) have been observed in these patients [2] and may ultimately be useful as diagnostic biomarkers of cutaneous vesicant injury.

Cellular, epidemiological, and toxicological evidences indicate a causal association between SM exposure and increased incidence of lung and skin cancers [11,12,13,9,25,16]. The association also likely extends to leukemia. Accurate estimates of potential cancer risk are limited due to the lack of exact and detailed information about mustard gas exposure [24]. Given that the risks associated with cancer cannot be measured accurately at mentioned period, and usually requires longer time (about 35–45 years), exact and regular examination – usually within three months- for evaluation of potential cancers is strongly recommended [3].

Our analysis has some limitations. It was a descriptive study in nature and therefore does not imply any causation. In addition, since this study only examined SM-exposed individual with severe ophthalmologic complications –a subgroup that may be independently associated with greater doses of SM exposure- the results cannot be generalized to all chemical victims. Further study with a larger sample including all survivors is needed in order to confirm the relationships between early and late skin complications in all sulfur mustard chemical victims. In addition, we did not study the relation of any type of pulmonary complications in this study. It is recommended to assess the association of early and late skin manifestations, to find out the relation of the pulmonary complications and its severity on late skin features.

5. Conclusion

Our study showed that the prevalence of pruritis, xerosis, pigmentation changes, cherry angioma, and burning were more associated with the presence of early blister and erythema (two important risk factors) in SM exposed survivors with severe ocular complications. The genitalia and great flexure areas were the most commonly involved anatomical sites for both early and late skin lesions in these SM exposed survivors.

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Transparency document

The Transparency document associated with this article can be found in the online version.

Conflicts of interest

The authors have no conflicts of interest, financial or otherwise, related to this study.

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