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Lung Ultrasound Accuracy in Respiratory Distress Syndrome and Transient Tachypnea of the Newborn

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Key Words
Lung ultrasound · Neonate · Respiratory distress syndrome · Transient tachypnea of the newborn

Abstract
Background: Lung ultrasound (LUS) is a promising technique for the diagnosis of neonatal respiratory diseases. Preliminary data has shown a good sensitivity and specificity of LUS in the diagnosis of respiratory distress syndrome (RDS) and transient tachypnea of the newborn (TTN). ***Objective:*** The aim of this study was to calculate the sensitivity, specificity, and negative (NPV) and positive predictive value (PPV) of LUS for RDS and TTN, using an external reader blinded to the clinical condition. ***Design and Methods:*** Neonates with respiratory distress had a LUS within 1 h of admission. Images were uploaded and sent to the external reader, who made the ultrasound diagnosis according to the appearance of the images. The final clinical diagnosis was made according to all the available data, except LUS data. Sensitivity, specificity, PPV, and NPV were calculated considering the final clinical diagnosis as the gold standard. ***Results:*** Fifty-nine neonates were studied (mean gestational age: 33 ± 4 weeks, mean birth weight: 2,145 ± 757 g). Twenty-three infants had a final diagnosis of RDS and 30 of TTN. LUS showed a sensitivity of 95.6% and specificity of 94.4%, with a PPV of 91.6% and a NPV of 97.1% for RDS, and a sensitivity of 93.3% and specificity of 96.5% with a PPV of 96.5% and a NPV of 93.4% for TTN. ***Conclusions:*** LUS showed high sensitivity and specificity in diagnosing RDS and TTN.

Introduction

Respiratory distress is a common cause of admission to the neonatal intensive care unit. The most prevalent lung diseases are respiratory distress syndrome (RDS), and transient tachypnea of the newborn (TTN) [1–4]. Both can present with similar signs and the standard management includes evaluation of chest X-rays (CXR). However, distinguishing RDS and TTN may be difficult during the first 24 h after birth [5].

Lung ultrasound (LUS) may be a tool for the differential diagnosis of respiratory distress in newborns. We previously described that specific ultrasound changes can have sensitivity and specificity as high as 100% in the diagnosis of RDS and TTN [6, 7]. Our data may have been biased because the operators were not blinded even if not involved in the clinical management. The aim of this study was to determine the diagnostic accuracy of LUS in the evaluation of RDS and TTN, submitting the images to an external reader blinded to the clinical condition.

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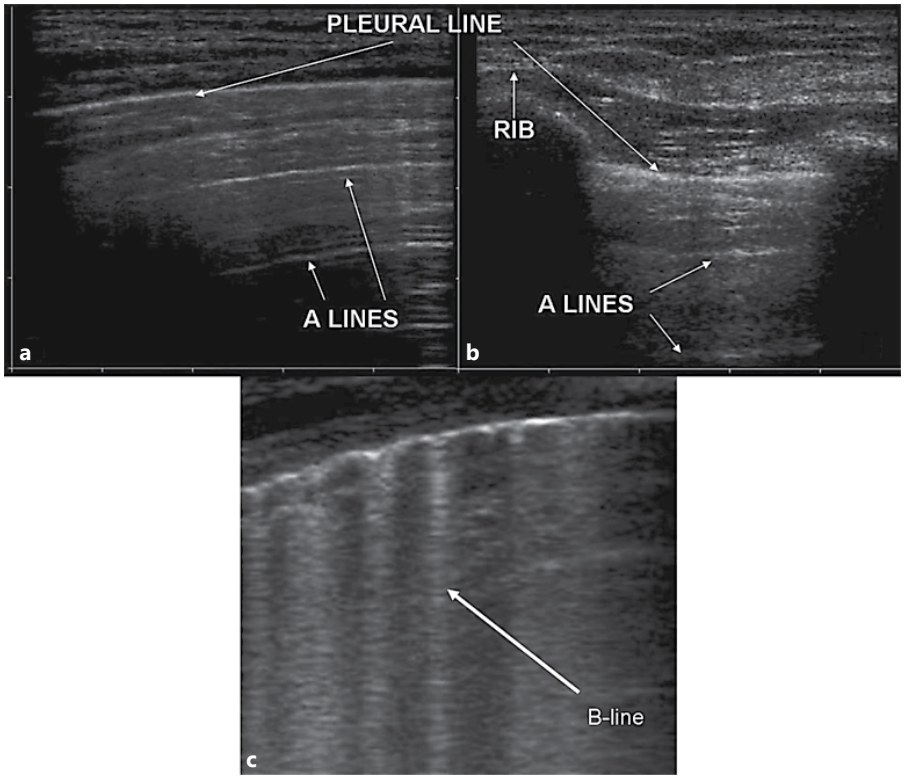

Fig. 1. Normal echographic anatomy of the lung. **a** Transversal scan. **b** Longitudinal scan. Note the regular pleural line, the presence of A-lines, and, in the longitudinal scan, the acoustic shadow of the ribs (arrows). **c** Close-up of the B-line appearance. B-lines project from the pleural line to the edge of the screen, erase A-lines, and move with respiration.

Methods

Study Design and Settings

Newborns admitted for respiratory distress were screened for enrollment in this prospective cohort study. The neonates were recruited between January 2011 and June 2011. LUS was done within 1 h after admission by a trained neonatologist (internal referee). The operator was aware of the clinical status of the patient. The images were always stored in the same manner (midclavicular right, midaxillary right, midclavicular left, and midaxillary left) and then sent in this sequence to the external referee (unaware of the clinical history) who made the ultrasound diagnosis. The final clinical diagnosis was made by a single neonatologist (not involved in the LUS examination) according to all the available data, but without the ultrasound data. A chest radiography was part of the workup for respiratory distress if considered necessary by the physician in charge of the infant. To evaluate the diagnostic accuracy of LUS, we compared ultrasound diagnosis to the clinical diagnosis, considering the latter as the gold standard.

The study was approved by our local ethical committee, although LUS is a standard procedure for all the infants showing respiratory distress.

Inclusion Criteria

Neonates with respiratory distress that started within the first 24 h after birth were included if they showed at admission signs of respiratory distress defined as: respiratory rate >60 breaths/min, FiO_2 requirement >0.21, intercostal/subcostal retractions, grunting, and/or nasal flaring. An oxygen saturation target of 90–95% was considered appropriate.

Exclusion Criteria

Patients with a diagnosis of a major congenital malformation, structural heart disease, or chromosomal diseases/syndromes were not enrolled.

LUS Procedure

LUS was done with Vivid-i (GE Medical Systems, Milan, Italy) using a high-resolution 10–12 MHz linear probe, with a dedicated preset. The examination was performed at bedside while the supine newborn was in an incubator or under a radiant warmer. Two longitudinal sections of each hemithorax were examined: one anterior area delimited by parasternal and anterior axillary lines (midclavicular scan) and one lateral area between the anterior and posterior axillary lines (midaxillary scan).

Ultrasound Diagnosis

In a normal lung the pleura appears as a regular echogenic line moving continuously during respiration [8]. Beyond the pleura, the lung is filled with air and does not allow further visualization of normal lung parenchyma. The large change in acoustic impedance at the pleura-lung interface results in horizontal artifacts, defined as A-lines, that are seen as a series of echogenic parallel lines distally and are equidistant from one another [9] (fig. 1).

Vertically oriented artifacts, called B-lines (fig. 1), indicate an abnormality in the interstitial or alveolar compartment and correlate with lung interstitial fluid content [10]. B-lines project from the pleural line to the edge of the screen, erase A-lines, and move with respiration [11]. Because the fetal lung has a high fluid content, B-lines can be seen in the first day of life also in neonates without respiratory distress [12].

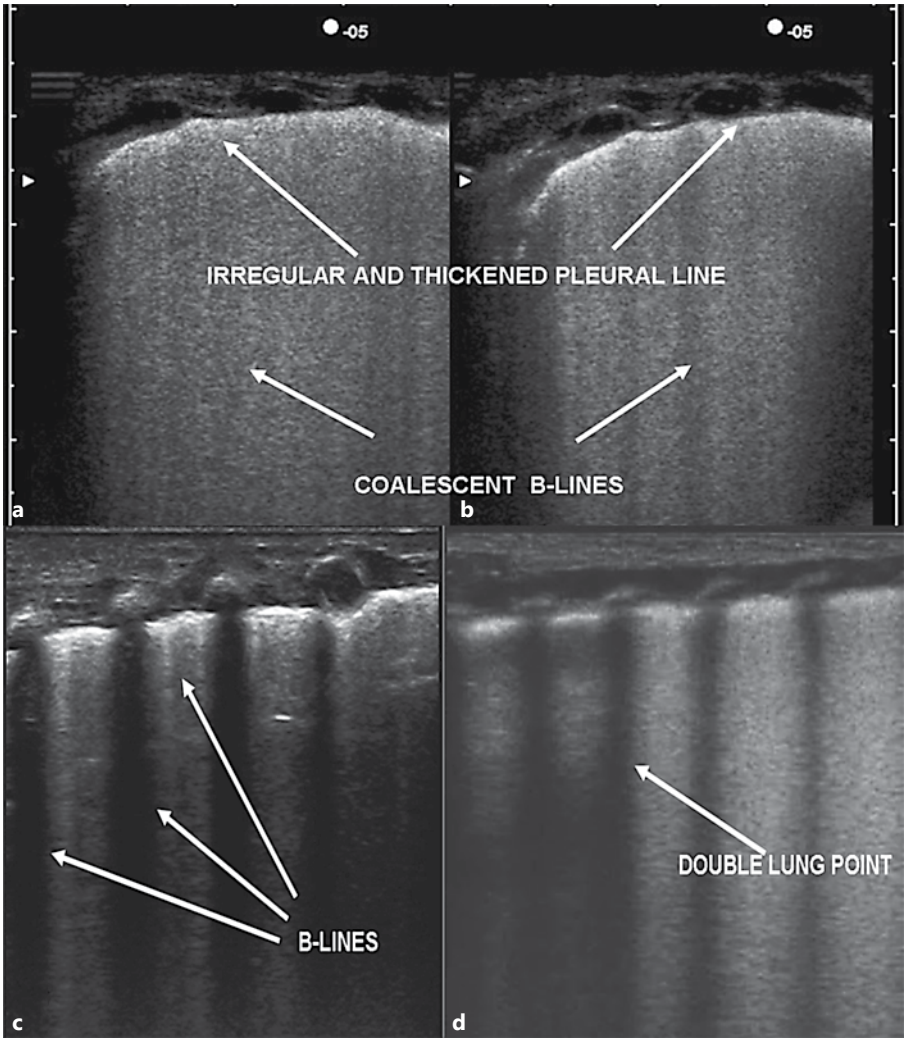

Fig. 2. LUS appearance of RDS and TTN. **a**, **b** RDS: bilateral evidence of echographic 'white lung' (coalescent B-lines), thickened and irregular pleural line (arrow), and absence of spared areas. **c** TTN: presence of numerous noncompact B-lines indicating interstitial engorgement (arrows). **d** TTN: presence of very compact B-lines in the inferior pulmonary field and normal appearance in the superior field (double lung point, arrow).

Sonographic diagnosis of RDS was based on bilateral white lung (coalescent B-lines from base to apex) without spared areas, associated at a thickened and irregular pleural line [6] (fig. 2). TTN diagnosis by ultrasound was defined as a normal pleural line and pleural sliding, associated with the presence of very compact B-lines in the inferior pulmonary fields and less compact B-lines in the superior fields (double lung point) in both lungs, or bilateral presence of numerous noncompact B-lines indicating interstitial engorgement [7] (fig. 2).

Clinical Diagnosis

A diagnosis of RDS was made if the clinical course and the CXR appearance were consistent and there were no positive group B Streptococcus cultures. We considered typical abnormalities of RDS the radiographic presence of diffuse atelectasis, 'ground glass' appearance of the lung fields, and air bronchograms. TTN was diagnosed when the oxygen requirements and respiratory support were mild or moderate, the clinical condition improved within the first 72–96 h after birth, and CXR (if done) appearance was consistent. We considered radiological features suggestive of TTN prominent perihilar vascular markings, edema of the interlobar septae, fluid in the fissures, and hyperinflation. Diagnosis was based on all the above conditions for both RDS and TTN.

Statistical Analysis

Continuous variables are reported as mean ± SD. The statistical analysis was performed with the use of SAS software for Windows, version 9.3 (SAS Institute Inc., Cary, N.C., USA).

Nonparametric continuous variables (gestational age, neonatal weight, APGAR values at 1st and 5th min) in the RDS and TTN groups were compared by using a Wilcoxon test. The significance was set at $p < 0.05$ for each variable. Fisher's exact test was used for comparison of categorical variables: final diagnosis (RDS or TTN) and respiratory assistance. $p < 0.05$ was considered significant.

Sensitivity was defined as the number of true positives/(number of true positives + number of false negatives); specificity as the number of true negatives/(number of false positives + number of true negatives); positive predictive value (PPV) as the

number of true positives/(number of true positives + number of false positives), and negative predictive value (NPV) as the number of true negatives/(number of true negatives + number of false negatives).

Results

Fifty-nine patients were identified and enrolled in the study: 36 (61%) were males and 14 (24%) were twins. The gestational age of the subjects ranged from 23 to 41 weeks (33 ± 4 weeks, mean ± SD). The mean birth weight was 2,146 ± 758 g. The distribution of the diseases defined with the gold standard (clinical and nonultrasound data) is presented in table 1.

Table 2 shows the demographics and the respiratory assistance features of the infants with RDS (n = 23) and TTN (n = 30). The infants of the RDS group had, as expected, a significantly lower birth weight, gestational age, and Apgar score at 1 and 5 min.

CXR was performed in all 23 infants with RDS and in 19 in the TTN group. CXR was considered consistent with the final diagnosis of TTN in 17 cases with 2 false positives, while in the RDS group CXR coincided with the final diagnosis in 21 cases with 3 false positives. CXR showed a sensitivity of 91.3%, a specificity of 84.2%, a PPV of 87.5% and a NPV of 88.8% for RDS, and a sensitivity of 89.4%, a specificity of 91.3%, a PPV of 89.4%, and a NPV of 91.3% for TTN (table 3).

LUS was consistent with the final diagnosis of TTN in 28 of 30 cases, with 1 false positive, while in the RDS group LUS coincided with the final diagnosis in 22 of 23 cases with 2 false positives. LUS showed a sensitivity of 95.6%, a specificity of 94.4%, a PPV of 91.6%, and a NPV of 97.1% for RDS, and a sensitivity of 93.3%, a specificity of 96.5%, a PPV of 96.5%, and a NPV of 93.4% for TTN (table 3). LUS diagnosis did not match the final clinical diagnosis in 3 cases (1 in TTN group and 2 in RDS group): the final diagnosis was pneumonia for the TTN case, and pneumonia and meconium aspiration for the 2 RDS cases (fig. 3).

Table 1. Distribution of final diagnoses

Final diagnosis	
RDS	23 (39)
TTN	30 (51)
Pneumothorax	1 (2)
Meconium aspiration	2 (3)
Neonatal pneumonia	2 (3)
Atelectasis	1 (2)
Total	59

Values represent n (%).

Table 2. Demographic data and type of respiratory support (RDS patients vs. TTN patients)

	RDS patients (n = 23)	TTN patients (n = 30)	p
Birth weight, g	1,616±604	2,442±609	<0.001
<1,000	3 (13)	0 (0)	
1,000–1,499	8 (35)	4 (13)	
1,500–2,499	10 (43)	14 (47)	
≥2,500	2 (9)	12 (40)	
Gestational age, weeks	30.3±3.7	34.5±2.6	<0.001
<24	1 (4)	0	
24–26	3 (13)	0	
27–29	4 (17)	2 (7)	
30–32	9 (39)	3 (10)	
33–35	5 (23)	17 (57)	
>35	1 (4)	8 (26)	
Apgar score:			
1 min	6±2.1	7.2±1.2	<0.02
5 min	7.4±1.5	8.3±1	<0.03
Surfactant therapy	23 (100)	0	
Life hours	9.8±12.4	–	
Respiratory assistance			
CPAP	4 (18)	24 (80)	<0.001
Mechanical ventilation	9 (39)	3 (10)	<0.01
HFOV	10 (43)	0	–
Other	0	3 (10)	–

Values represent means ± SD or n (%).

Discussion

In this study LUS showed a high diagnostic accuracy for RDS and TTN in neonates with early respiratory distress. It is important to distinguish RDS and TTN because of the prognostic and therapeutic implications. RDS affects mainly preterm infants [13] and surfactant replacement therapy [14, 15], as well as dedicated respiratory support improves outcomes [2–4]. The presenting symptoms are similar in both pathologies and distinguishing the two entities may be difficult even with CXR [5].

LUS evaluates the artifacts generated by the reflection of the ultrasound beam at the pleural/subpleural interface.

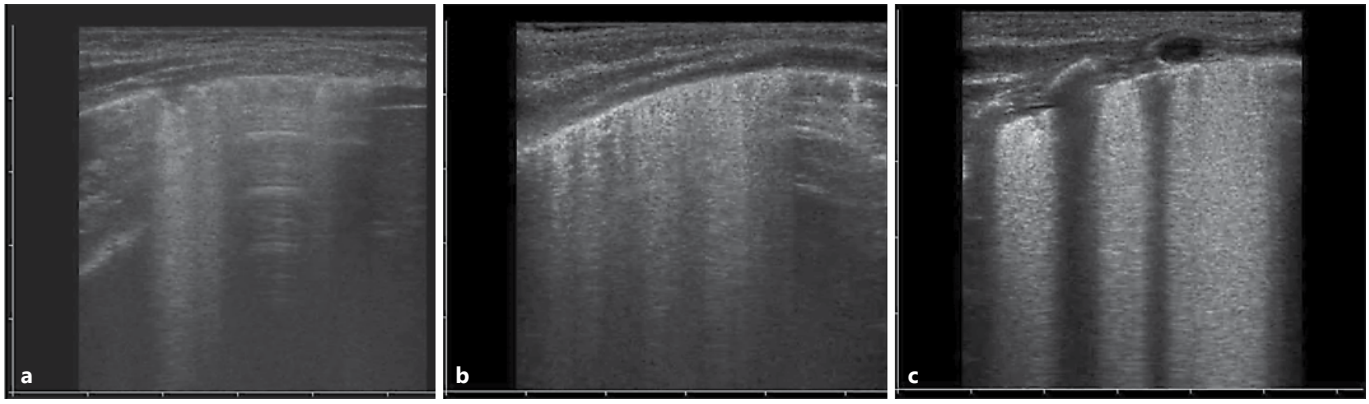

Fig. 3. LUS diagnosis did not match the clinical diagnosis in 3 cases (1 in the TTN group and 2 in the RDS group). For the case in the TTN group, the final diagnosis was pneumonia (**a**); for the 2 cases in the RDS group, the final diagnosis was pneumonia (**b**), and meconium aspiration (**c**).

It has shown a significant correlation with extravascular lung water in both adults [16, 17] and neonates [18]. Avni et al. [19] described lung retrohepatic anomalies at abdominal ultrasonography in newborns with RDS, but evaluation by the transabdominal approach cannot show lung apex involvement and pleural changes that are essential to distinguish RDS from TTN [7]. We previously described the specific LUS findings in neonates with RDS [6] or TTN [7] through the transthoracic approach.

RDS presents as a sonographic white lung, associated with an irregular pleural line and absence of spared areas (fig. 2). Sonographic abnormalities precede PaO_2/FiO_2 changes [6, 20] and, unlike CXR, sonographic appearance of RDS does not change immediately after surfactant administration. This may be related to the immaturity of the interstitial space that is not affected by the exogenous surfactant administration. In an animal model we demonstrated that the clearance of lung fluid does not improve after surfactant administration, and there is no difference in fluid lung content among lungs treated or not treated with surfactants [18]. This explains why there are no changes in the LUS picture immediately after surfactant administration. The sonographic evolution of the RDS LUS pattern was heterogeneous. In some infants the areas of 'white lung' and pleural changes persisted for several weeks, while in others the evolution was faster with reduction of 'white lung' areas and pleural line abnormalities within 1 week. However, in all the infants of the RDS group, some degree of 'white lung' was present up to 36 weeks after conception.

The typical finding of TTN at LUS is the 'double lung point' (fig. 2), which is the result of coalescent B-lines in the inferior pulmonary fields, while in the superior fields

Table 3. Sensitivity, specificity, PPV, and NPV of LUS and CXR for RDS and TTN

	RDS	Other	Total
CXR positive	21	3	24
CXR negative	2	16	18
Total	23	19	42

Sensitivity: 91.3%; specificity: 84.2%; PPV: 87.5%; NPV: 88.8%.

	TTN	Other	Total
CXR positive	17	2	19
CXR negative	2	21	23
Total	19	23	42

Sensitivity: 89.4%; specificity: 91.3%; PPV: 89.4%; NPV: 91.3%.

	RDS	Other	Total
LUS positive	22	2	24
LUS negative	1	34	35
Total	23	36	59

Sensitivity: 95.6%; specificity: 94.4%; PPV: 91.6%; NPV: 97.1%.

	TTN	Other	Total
LUS positive	28	1	29
LUS negative	2	28	30
Total	30	29	59

Sensitivity: 93.3%; specificity: 96.5%; PPV: 96.5%; NPV: 93.4%.

the B-lines are present but not coalescent or even absent. The border between the inferior fields where the B-lines are coalescent and the superior fields is so sharp that the LUS picture is specific [7]. A possible interpretation of the 'double lung point', revealing a higher water content at the bases compared to apical regions, may be done recalling the dynamics of lung water drainage in the postnatal hours. Most extravascular water (alveolar plus interstitial) accumulates in the most dependent parts of the lung due to gravity. Following fluid reabsorption from alveoli to the extravascular interstitial space, hydraulic pressure increase remarkably in the latter, sustaining a passive Starling-dependent flow into the capillaries. This mechanism likely accounts for about 90% of lung water clearance in the first postnatal hours. The echographic evolution of the double lung point was consistent with the clinical evolution of the disease and disappeared in 72–96 h. We found the double lung point in 20 out of 28 infants in which LUS was consistent with TTN, while in the remaining 8 the pattern of diffuse noncoalescent B-lines was present. In these 8 patients, the echographic picture also cleared to a nearly normal appearance accordingly with the clinical evolution in 72–96 h.

Data from our previous study may have been biased because the operators were not blinded to clinical status. In the current study the external referee, unaware of the clinical history and examination findings, made the ultrasound diagnosis according only to the appearance of the stored images taken by an internal operator that was aware of the clinical status of the patient. We obtained a high specificity and sensitivity in RDS (94.4 and 95.6%, respectively) and TTN (96.5 and 93.3%, respectively). The PPV and NPV are also interesting, with 91.6 and 97.1%, respectively, in RDS and 96.5 and 93.4%, respectively, in TTN. This suggests that RDS or TTN can be excluded in the absence of typical LUS findings.

Even if preliminary data suggest a PPV of 100% in detecting pulmonary complications of RDS [21], LUS cannot evaluate some air leak syndromes (interstitial emphysema, pneumomediastinum, pneumopericardium) and thus, cannot replace CXR completely in respiratory distress workup. However, LUS is a noninvasive exam that adds meaningful data not achievable with CXR, and radiation exposure early in life can be reduced by its application [22].

Our study has some limitations. The number of the subjects studied is limited and we did not evaluate some other causes of respiratory distress. However, the sample included the prevailing neonatal respiratory diseases, and rare pathologies in any case require deeper evaluation.

The agreement between clinicians in radiography evaluation is thought to be low, especially concerning TTN findings [5]. Indeed, in our patients, sensitivity and specificity of CXR was good. However, not all the patients with TTN had a CXR performed and this may have biased the results.

Finally, it may be difficult to define the normal neonatal lung appearance because B-lines can also be seen in healthy newborns in the first hours after birth [6]. However, the use of LUS is clinical and therefore a newborn without respiratory signs is not supposed to be scanned by LUS, which in fact minimizes the risk of a mistake. Moreover, the external referee had a good ability to distinguish between a normal lung appearance and a pathologic 'wet lung', as demonstrated by the sensitivity and specificity data. Further studies with a larger number of patients are needed to compare CXR and LUS findings, and validate the technique in a larger population. However, our findings present new evidence about LUS reliability which may complete the standard diagnostic approach to respiratory distress in newborns.

Conclusion

LUS is a reliable method to diagnose RDS and TTN in newborns with respiratory distress, and in our experience shows a high sensitivity and a specificity comparable with CXR.

Disclosure Statement

The authors have no conflicts of interest to disclose. No external funding was secured for this study. The authors have no financial relationships relevant to this article to disclose.

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