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ORIGINAL ARTICLE

Developing a clinical scoring system to differentiate deep-seated atypical lipomatous tumor from lipoma of soft tissue

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Summary *Background:* Atypical lipomatous tumor (ALT) is a low-grade malignancy that frequently occurs at a subfascial anatomical location. While marginal excision is adequate for lipomas, excision with a surgical margin is suggested for ALTs. However, ALTs and lipomas are difficult to differentiate preoperatively, even with the help of imaging studies. In this study, we aimed to formulate a scoring system based on selected clinical and imaging characteristics to enhance the accuracy of pre-operative diagnosis of deep-seated ALTs.
Methods: We enrolled 417 cases of deep-seated lipoma and 53 cases of ALTs from soft tissue treated between 2005 and 2016. Tumors arising from the bone, internal cavities, retroperitoneum, or nervous system were excluded. Clinical data were analyzed along with magnetic resonance image (MRI) features. We further developed a scoring formula to distinguish deep-seated ALTs from lipomas.
Results: Older age, tumor location at lower limbs, and the presence of MRI features (larger size, thick septa $>$ 2 mm, contrast enhancement$>$1 cm, fat component $<$75%) are identified as risk factors of ALT and were utilized to develop a scoring system for distinguishing ALTs from lipomas. The formula exhibited 90% sensitivity and 92.5% specificity, and a score more than 0.214 suggested a diagnosis of ALT.

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Conclusions: The scoring system developed in this study can facilitate the pre-operative diagnosis of deep-seated ALTs and lipomas. If ALT is suspected, further tumor biopsy followed by molecular diagnosis can establish a definite diagnosis. Therefore, this scoring system can serve as a cost-effective tool for the clinical management of deep-seated lipomatous tumors.

1. Background

Lipoma is the most common soft tissue tumor which may occur at any anatomical location. Most lipomas are small, well-defined, and superficial subcutaneous tumors. On the contrary, deep-seated (subfascial) lipomas are usually infiltrative, larger in size, and much less common, accounting for only approximately 1% of all lipomas.[1,2] Pre-operatively, lipomas are difficult to distinguish from atypical lipomatous tumors (ALTs), previously referred as well-differentiated liposarcoma. ALT is a type of lipomatous tumor with atypical changes in histology. Although ALT is a low-grade mesenchymal neoplasm with a very low risk of distant metastasis, it is usually locally aggressive with a higher risk of local recurrence. Since inter- or intramuscular ALTs are more common, treatment of deep-seated lipomatous tumors poses a greater challenge to surgeons.[3]

Wide resection of deep-seated ALTs may lead to more surgical complications, so some surgeons have suggested marginal resection as an appropriate treatment for ALT.[4] However, ALTs have been reported to show a significantly higher recurrence rate than lipomas,[5] and they also exhibit a potential to dedifferentiate into high-grade liposarcoma over time.[6–8] Therefore, it is more appropriate to establish a surgical margin beyond the marginal resection border, and muscle resection should be performed to the extent which would not greatly reduce muscle strength.[9] Since excision with a surgical margin is more challenging for subfascial tumors, the accurate pre-operative diagnosis of deep-seated ALTs or lipomas is critical for surgeons to choose adequate surgical approaches for the tumor. The histology finding of ALT usually shows mature adipose tissue punctuated with large atypical hyperchromatic cells. The predominant fatty component and low cellularity of ALTs renders the pathological examination of their core biopsy samples unreliable. Pathological diagnosis can be challenging because the atypia may present focally and be easily missed.[10] Although an accurate diagnosis of ALT can be made by fluorescent in situ hybridization (FISH) via characterizing the amplification of *MDM2* and *CDK4* genes,[10–12] it is not cost-effective to perform a biopsy and FISH exam for every case of deep-seated lipomatous tumor.

Several studies have evaluated various clinical risk factors to differentiate ALTs from lipomas, such as tumors larger than 10 cm in size, located in the thigh, or found in patients over 60 years old.[12,13] Moreover, imaging studies have been employed to offer some references pre-operatively. Ultrasonography is an inexpensive and widely available imaging tool, but it has limited capability in differentiating lipomas from ALTs, especially for large tumors with inhomogeneous echogenic patterns.[14] Both computed tomography and magnetic resonance imaging (MRI) are better modalities for soft tissue tumors, and MRI is particularly useful for differentiating liposarcoma from lipoma.[15] However, the accuracy of imaging diagnosis by MRI is still not ideal; experienced observers without standardization criteria could only differentiate ALT from lipoma in 69% among the cases of pathologically proven lipomas ($n = 31$) and ALTs ($n = 29$).[16]

Previous studies have identified several MRI features favoring a diagnosis of liposarcoma that can be readily interpreted by non-radiologist physicians, including thick septa (>2 mm),[14,17–19] nodular enhancing area larger than 1 cm,[14] or lesser than 75% of fat component.[14,17] By combining the clinical and image findings, a more accurate pre-operative diagnostic tool of deep-seated ALTs may be developed. However, previous clinical studies addressing this issue exhibited limited case numbers, and they did not focus on deep-seated lipomatous tumors.[20,21] Herein we aimed to review the medical records in our institute to generate a more comprehensive pre-operative evaluation tool to differentiate deep-seated ALTs from lipomas. The development of this diagnostic tool will assist surgeons to decide whether biopsy and molecular testing are needed to confirm the diagnosis of ALT before proceeding to surgical excision.

2. Patients and methods

2.1. Subjects

We retrospectively identified all deep-seated ALT or lipoma cases that were confirmed by surgical pathology between 2005 and 2016 in National Taiwan University Hospital, a 2200-bed, university-affiliated medical center which provides both primary and tertiary referral care in Northern Taiwan. The study protocol was approved by the Institutional Review Board of National Taiwan University Hospital. Deep-seated tumors were defined as tumors locating underneath the muscle fascia level, such as intra- or intermuscular tumors. Tumors arising from the bone, retroperitoneum, internal cavities, and nervous system, such as lipomyelomeningoceles, were excluded. Recurrent or residual tumors were also excluded.

2.2. Clinical data

All patients underwent surgical excision, and the diagnosis of ALT or lipoma was established by pathology. Clinical information that had been previously described as risk factors

associated with ALT was collected from the patients' medical records, including age, sex, and tumor location. Due to the limited case number, the tumor locations other than upper and lower limbs were categorized into an "other" group for further analysis. MRI findings were re-evaluated by two radiology specialists independently without knowing the pathological diagnosis. The tumor size was determined by measurements of the greatest tumor dimension on MRI. According to previous publications,[14,17–19] three major MRI criteria for suspected ALT were also evaluated: thick septa structure (>2 mm), less than 75% fat component and a nodular dominant focus (>1 cm enhancing area; Fig. 1).

2.3. Statistical analysis

All data are presented as means ± standard deviation. The demographic and clinical characteristics were compared between the ALT and lipoma group by Student's t-test for continuous variables, and chi-square test or Fisher exact test for categorical variables. The univariate logistic regression analysis was applied first to estimate the odds ratio (OR) and 95% confidence interval (CI) of the clinical and MRI variables for the risk of ALT, taking lipoma as the reference group. The variables with $p < 0.05$ in the univariate analysis were selected into the multivariable logistic regression model. Using the coefficients in the multiple model and the factors of each patient, the probability of ALT was calculated for each patient. Finally, the analyses of the receiver operating characteristic (ROC) curve and the area under the curve (AUC) were conducted using the probabilities of all patients. The cut-off of probability for predicting ALT was decided by Youden's index, which was derived from the calculated sensitivity and specificity. All data analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

From 2005 to 2016, we identified 1966 cases of lipoma and 223 cases of liposarcoma, and 417 cases and 81 cases of them were deep-seated lipoma and liposarcoma, respectively. Among the 81 cases of deep-seated liposarcoma, 53 had a pathological diagnosis of ALT (Fig. 2). The patients with deep-seated ALTs were significantly older than those with lipomas (59 ± 13.33 vs. 52 ± 14.87 years, $p < 0.001$), and the male-to-female ratio was significantly higher in the ALT group (62.3% vs. 47.5%, $p = 0.043$). Deep-seated ALT tended to locate at the lower extremity, while lipomas were more likely to occur at places other than the limbs ($p < 0.001$). Of the 470 patients, only 208 received MRI examination. In MRI characteristics, the tumor size was significantly larger in ALT cases than lipoma cases (14.49 ± 7.30 vs. 6.77 ± 4.05 cm, $p < 0.001$); the other three selected criteria also showed a significant difference between the deep-seated ALT and lipoma groups ($p < 0.001$ respectively; Table 1).

Two of the MRI characteristics (>1 cm contrast enhancement and <75% fat component) were combined into one parameter for univariate analysis to achieve the

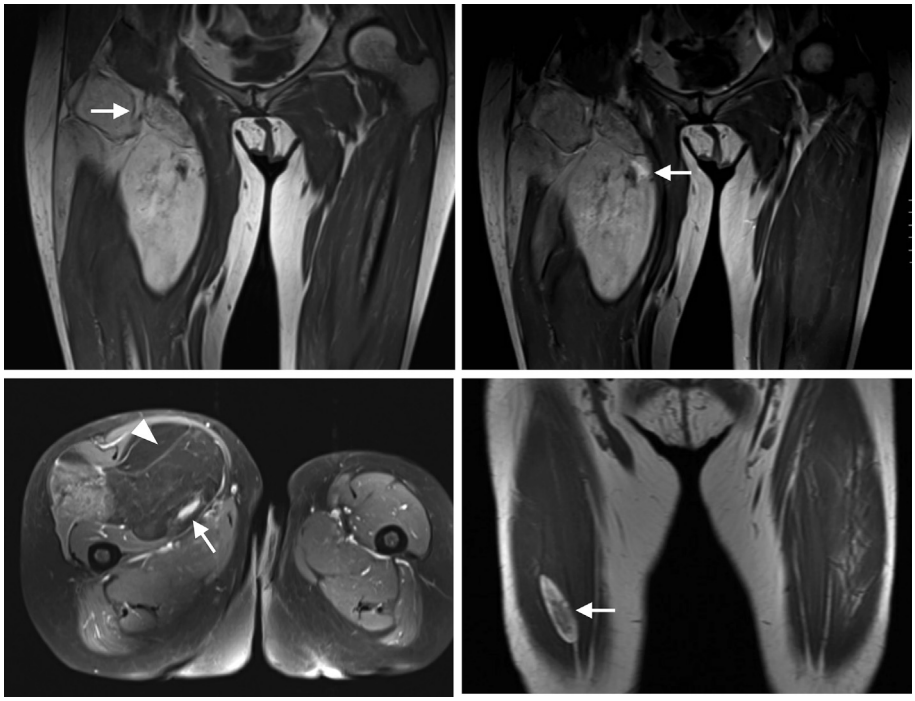

Figure 1 Representative features of ALT on MRI employed in this study. (*Left above*) The arrow indicates thick septum (>2 mm) in a coronary T1-weighted image. (*Right above*) The arrow indicates a nodular contrast-enhanced area (>1 cm). (*Left below*) The arrow indicates s a nodular contrast-enhanced area (>1 cm) and the arrowhead shows a thick septum (>2 mm) in an axial T1-weighted and contrast-enhanced fat-suppression T1-weighted image. (*Right below*) The arrow indicates less than 75% fat component in a coronary T1-weighted image.

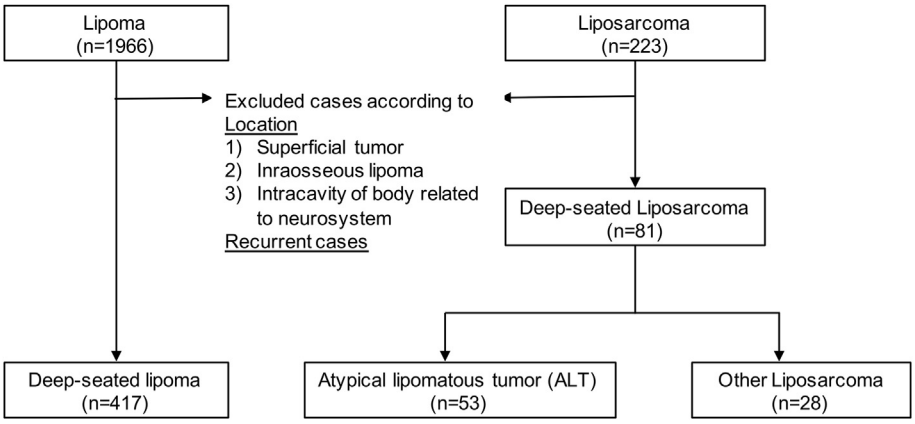

Figure 2 Algorithm of case selection among lipomatous tumors in this study.

optimal prediction value. Univariate analysis showed that the clinical factors that were significant in differentiating deep-seated ALTs from lipomas included age, sex, and location ($p < 0.05$). The selected MRI parameters also yielded significant difference: larger tumor size (OR, 1.32; 95% CI, 1.23—1.41 $p < 0.001$), thick septa > 2 mm (OR, 14.3; 95% CI, 6.11—33.49; $p < 0.001$), and >1 cm contrast enhancement or < 75% fat component on MRI (OR, 32.23; 10.26—101.23; $p < 0.001$; Table 2). We then incorporated all the aforementioned factors into a multivariable regression model (Table 2). Based on the OR garnered from the multivariate analysis, we further developed an easy-to-use diagnostic tool to predict whether a deep-seated lipomatous tumor is lipoma or ALT (Table 3). A ROC curve was plotted and the AUC was 0.93 indicating strong power for the scoring system to discriminate ALT from benign lipoma. The maximal Youden's index was 0.825 with 90% sensitivity and 92.5% specificity (Fig. 3).

4. Discussion

Lipomatous tumor constitutes the largest single group of soft tissue tumors,[1,2] and liposarcoma is the most common soft tissue sarcoma, which accounts for one-third of this kind of lesion.[22,23] ALT accounts for 40—45% of liposarcomas and is the most prevalent subtype of liposarcoma.[24] ALT tends to occur in deep location of soft tissue, and it has been estimated that 25% of deep-seated lipomatous tumors in the extremity or trunk wall are ALTs.[25] Compared to superficial soft tissue tumors, deep-seated lesions are more

Table 1 Demographic characteristics and MRI features of deep-seated lipoma and ALT patients.

	Lipoma	ALT	p-value
Clinical parameters	n = 417	N = 53	
Age	52.3 ± 14.87	59.6 ± 13.33	<0.001
Sex			
M	198 (47.5%)	33 (62.3%)	
F	219 (52.5%)	20 (37.7%)	0.043
Location			
Lower limb	69 (16.5%)	35 (66.0%)	<0.001
Upper limb	137 (32.9%)	10 (18.9%)	
Other	211 (50.6%)[a]	8 (15.1%)[b]	
MRI parameters			
Size (cm)	n = 174	n = 34	
	6.77 ± 4.05	14.49 ± 7.30	<0.001
Thick septa >2 mm	n = 174	n = 34	
None	149 (85.6%)	10 (29.4%)	<0.001
Present	25 (14.4%)	24 (70.6%)	
<75% fat component	n = 174	n = 34	
None	170 (97.7%)	24 (70.6%)	<0.001
Present	4 (2.3%)	10 (29.4%)	
Enhancing area>1 cm	n = 146	n = 30	
None	144 (98.6%)	15 (50%)	<0.001
Present	2 (1.4%)	15 (50%)	

[a] Other locations of lipoma: abdomen (n = 12), back (n = 105), chest (n = 30), and head and neck (n = 63).
[b] Other locations of ALT: back (n = 2), 2 cases over chest (n = 2), and head and neck (n = 4).

Table 2 Univariate and multivariate analysis of predictors for deep-seated ALT patients.

	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Clinical parameters				
Age	1.04 (1.02,1.07)	<0.001	1.03 (0.98,1.08)	0.209
Sex (M vs F)	1.82 (1.01,3.28)	0.045	1.99 (0.53,7.4)	0.306
Location				
Other vs Lower limb	0.08 (0.03,0.17)	<0.001	0.16 (0.02,1.19)	0.074
Upper limb vs Lower limb	0.14 (0.07,0.31)	<0.001	0.3 (0.06,1.52)	0.146
MRI parameters				
Size (cm)	1.32 (1.23,1.41)	<0.001	1.22 (1.07,1.4)	0.003
Thick septa > 2 mm	14.3 (6.11, 33.49)	<0.001	2.8 (0.63,12.45)	0.175
<75% fat component or Enhancing area>1 cm	32.23 (10.26,101.23)	<0.001	15.14 (1.95,117.68)	0.009

difficult to remove by wide excision with free margin and such a procedure may cause morbidities. Therefore, differentiation between deep-seated lipomas and ALTs is a crucial issue for surgical planning. Previous studies had analyzed various risk factors to facilitate the diagnosis of ALT from lipoma, such as older age,[12,13,21] deep-seated location,[20] tumor size >10 cm,[12,13,20,21] tumor at extremities or lower limbs,[12,13,21] presence of non-fatty areas,[11] and contrast enhancement on MRI.[20] In line with the previous studies, we selected 3 clinical parameters as well as 4 MRI findings and formulated a scoring system to differentiate deep-seated ALTs from lipomas. Particularly, tumor size could be more objectively and accurately determined by MRI study. The system exhibits a sensitivity of 90% and a specificity of 92.4%. The AUC is 0.93, indicating a strong power of the formula. Moreover, the calculation of the score can be easily accomplished using a computer spreadsheet or a web-based calculator (Appendix).

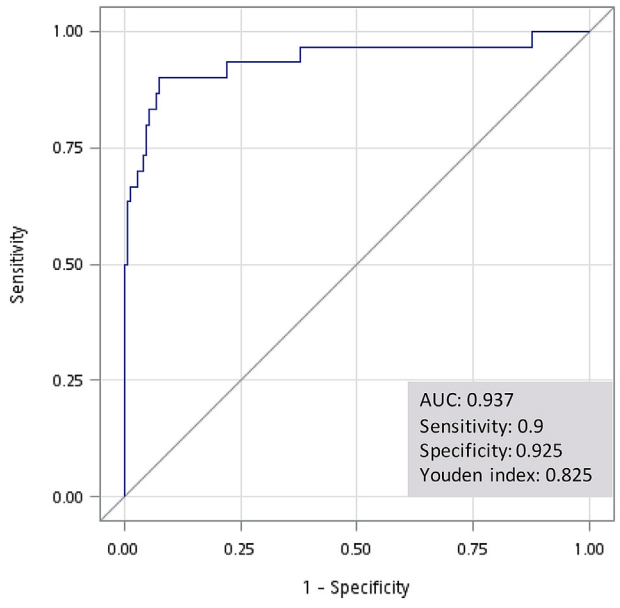

Figure 3 The receiver operating characteristic (ROC) curve of the scoring system to differentiate deep-seated atypical lipomatous tumor from lipoma. The area under the curve (AUC) of 0.980 indicates strong discriminating power. The maximum Youden index was 0.825 with.

Although some tumors may be large in size, asymptomatic lipomas do not necessarily require surgical excision. Even if surgery is considered, marginal resection is often adequate for lipoma. On the contrary, surgical removal is indicated for both asymptomatic and symptomatic ALT, though the appropriate surgical management is still controversial. No significant difference in the recurrence rate between patients receiving wide or marginal resection of ALTs was observed in a study,[26] and the recurrent rate was considered "acceptable" for marginal excision of soft tissue ALTs.[27] However, Errani et al estimated an recurrence rate of 13.9% for ALTs after marginal excision, thus suggesting a more aggressive surgical approach than marginal excision of the tumor.[5] In our opinion, while a relatively "conservative" surgery for deep-seated ALTs may be necessary to preserve major vessels or nerves,[4,9,28] a surgical margin beyond the marginal resection border is warranted whenever possible. Therefore, an accurate preoperative diagnosis of ALT is of paramount importance for appropriate surgical management of the deep-seated soft tissue ALTs.

ALTs may not be easily recognized by examining the morphological features in small biopsy samples due to the heterogeneity of the atypical cells. However, the development of FISH examination for *MDM2* and *CDK4* gene amplifications has unveiled a new era of accurate molecular diagnosis of ALT.[10–12,29] However, the technology requires special equipment and reagents, so it may not be available in every medical institution. Moreover, it may not be cost-effective to perform biopsy and FISH examination for every case with a deep-seated lipomatous tumor. Therefore, our scoring system provides an improved diagnostic tool to differentiate deep-seated ALTs from lipomas, thus facilitating preoperative planning for surgeons. Needle tumor biopsy followed by FISH exam for *MDM2* and *CDK4* gene amplifications in cases suspected to be ALT according to our scoring formula represents a more feasible and cost-effective method to obtain a definite diagnosis.

High-grade liposarcoma usually exhibits characteristic MRI findings and is easier to distinguish from lipoma.[14,19] The radiographic diagnosis of ALT is more challenging, and several MRI characteristics have been identified to

Table 3 The developed formula based on clinical parameters and MRI features to discriminate deep-seated ALTs from lipomas.

Formula

$$\log\left(\frac{P}{1-P}\right) = X = -6.1582 + 0.0312 * \text{Age} + 0.2020 * \text{Size} + 0.6862 * \text{Sex} - 1.8540 * \text{Other location} - 1.2003 * \text{Upper limb} + 1.0310 * \text{Thick septa} + 2.7176 * \text{Contrast enhancement} > 1\text{cm or fat component} < 75\%$$

$$\rightarrow P = \frac{\exp(X)}{1+\exp(X)}$$

The cut-off score: $P \geqq 0.214$, atypical lipomatous tumor is favored, otherwise lipoma is more likely

Parameters		
Age	Age (year-old) on diagnosis	
Size	Tumor maximum dimension (cm) measured on MRI	
	1	**0**
Sex	Female	Male
Other location	Tumor at other locations	Tumor at upper or lower limbs
Upper limb	Tumor at upper limbs	Tumor at lower limbs or other locations
Thick septa	Thick septa (>2 mm) presented on MRI	No thick septa on MRI
Contrast enhancement >1 cm or fat component <75%	Contrast enhancement >1 cm or fat component <75% on MRI	None of the presentation mentioned on MRI

facilitate the diagnosis of ALT, including thick septa (>2 mm),[14,17–19] nodular enhancing area larger than 1 cm,[14,19] and lesser than 75% of fat component.[14,17] Despite the aforementioned MRI features, the accuracy of a radiographic diagnosis is still not ideal for differentiating ALTs from lipomas. For example, in 60 patients with large (>5 cm), deep, pathologically proven lipomas or ALTs, only 69% was successfully differentiated by 10 observers who were experienced in musculoskeletal radiology and orthopedic oncology.[16] It is therefore reasonable to include both clinical and radiographic features for more accurate preoperative evaluation. However, to date, only one study had developed a weighted scoring system (0–6 point) to differentiate soft tissue ALT from lipoma. Nagano *et al.* included two clinical predictors (tumor size and depth of tumor) and two MRI characteristics (the presence of septal structures or contrast enhancement) in their formula, which was estimated to have 100% sensitivity and 77% specificity. However, their case number was limited with only 12 ALT and 18 lipoma cases.[20] In this study, we recruited more cases for analysis and excluded cases with superficial lesions that are usually benign lesions and easier to be excised with free margin. Hence, our scoring system represents a more comprehensive diagnostic tool when facing deep-seated ALTs and lipomas.

5. Conclusions

In the present study, we incorporated several clinical and MRI parameters that were identified as possible risk factors of ALT into a scoring system for differentiation of deep-seated soft tissue ALTs and lipomas. The clinical parameters are readily available: older age, tumor size >10 cm, lesions at lower limbs, and male gender. Particularly, the clinical and radiographic parameters used in the formula (thick septa >2 mm, contrast enhancement >1 cm, and less than 75% fat component) can be easily characterized by a non-radiologist. Based on the statistical analysis of these factors, we developed a formula to assist with the pre-operative diagnosis of ALT. If the calculated score is less than 0.214, lipoma is more likely, so follow-up monitoring or marginal resection is the treatment of choice. When the calculated score is more than 0.214, ALT is more probable and further tumor biopsy followed by FISH exam should be considered. Otherwise, direct tumor excision with a surgical margin can be performed whenever possible. Therefore, this scoring system represents an effective diagnostic tool to facilitate the differential diagnosis between deep-seated soft tissue ALTs and lipomas. Further validation of the formula in other cohorts is required to verify its clinical application.

Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.12.012.

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