

Original Article

Diagnostic value of TLE1 for synovial sarcoma: immunohistochemical analyses of genetically confirmed synovial sarcomas and nonsynovial sarcomas

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Abstract: Synovial sarcoma is a relatively common soft tissue malignancy that is characterized by a specific chromosomal t(X;18)(p11;q11) translocation. Transducin-like enhancer of split 1 (TLE1) has emerged as a useful marker for the diagnosis of synovial sarcoma. However, the diagnostic value of this antibody remains controversial. We investigated TLE1 expression in sixty-two fluorescence in situ hybridization-confirmed synovial sarcomas and three hundred twenty-two nonsynovial sarcomas using TLE1 immunohistochemical staining in tissue microarrays. Furthermore, the expressions of traditional immunohistochemical markers, including epithelial membrane antigen (EMA), AE1/AE3, CK7, Bcl-2 and CD99, were detected in the synovial sarcomas and compared with the expression of TLE1. The results showed that fifty-eight of the 62 (94%) synovial sarcomas were positive for TLE1. Twenty-four displayed 3+ staining (39%), 20 displayed 2+ staining (32%) and 14 displayed 1+ staining (23%). In contrast, 9% (30/322) of the nonsynovial sarcomas stained for TLE1 to various degrees. Notably, only 4% (12/322) of these tumors exhibited 2+ or 3+ staining, and these tumors included malignant peripheral nerve sheath tumors, solitary fibrous tumors, schwannomas and neurofibromas. Regarding the diagnosis of synovial sarcoma, the sensitivity and specificity of TLE1 were 94% and 91%, respectively. EMA staining was positive in 87% of the synovial sarcomas, Bcl-2 in 85%, AE1/AE3 in 61%, CK7 in 35% and CD99 in 24%. TLE1 is highly sensitive for synovial sarcomas and more sensitive than traditional immunohistochemical markers. This antibody can be used as a useful screening marker for synovial sarcomas, although complementary molecular studies remain the gold standards for this entity.

Keywords: Synovial sarcoma, TLE1, immunohistochemistry, fluorescence in situ hybridization, t(X;18), tissue microarray

Introduction

Synovial sarcoma is a morphologically, clinically, and genetically well-defined soft-tissue neoplasm that accounts for 5%~10% of all soft tissue sarcomas [1, 2]. Most tumors occur in the extremities near the joints in young adults. However, these tumors may occur at any age and have been reported to arise from a variety of unusual locations, such as the mediastinum, retroperitoneum, and various viscera [3, 4].

Histologically, synovial sarcomas can primarily be classified into monophasic, biphasic, and poorly differentiated subtypes. Monophasic synovial sarcomas most often consist of mono-

morphic spindle cells or epithelial cells. Biphasic synovial sarcomas have epithelial and fibroblast-like spindle cell components in various proportions. Poorly differentiated synovial sarcomas usually exhibit a round cell pattern [3, 4]. Due to their complex and diverse morphologies, synovial sarcoma (particularly the monophasic and poorly differentiated subtypes) can be confused with other soft tissue neoplasms, especially in small biopsy specimens. A panel of immunohistochemical markers, including Bcl-2, epithelial membrane antigen (EMA), cytokeratins, CD99, CD34, S-100 protein, and desmin, has been used to distinguish synovial sarcomas from other tumors in clinical practice. However, these markers cannot always arrive at a defini-

Table 1. Antibodies used for immunohistochemical examination

Antibody	Clone ID	Source	Antigen retrieval	Dilution	Dyeing system
TLE1	M-101	Santa Cruz	EDTA	1:100	EnVision
EMA	E29	Dako	Citric acid	1:100	EnVision
Cytokeratin	AE1/AE3	Dako	Citric acid	1:200	EnVision
CK7	OV-TL 12/30	Dako	Citric acid	1:100	EnVision
Bcl-2	124	Dako	Citric acid	1:200	EnVision
CD99	12E7	Dako	Citric acid	1:100	EnVision

tive diagnosis [5, 6]. Most synovial sarcomas are characterized by a specific chromosomal t(X;18)(p11;q11) translocation that leads to SS18-SSX gene fusion [7-10]. Therefore, the identification of t(X;18)(SS18;SSX) is considered the gold standard for the diagnosis of synovial sarcomas, and t(X;18)(SS18;SSX) can be detected by fluorescence in situ hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR), or cytogenetics. However, molecular studies have not been widely used in all laboratories.

Transducin-like enhancer of split 1 (*TLE1*) is one of four members of the *TLE* gene family and encodes transcriptional corepressors that are homologous to the *Drosophila groucho* gene [11, 12]. *TLE1* plays important roles in many signaling pathways, including cell survival, hematopoiesis, neuronal differentiation, and terminal epithelial differentiation pathways [11, 12]. Moreover, *TLE1* is involved in the Wnt/ β -catenin signaling pathway [13], which is known to be associated with synovial sarcomas [14, 15]. Recently, some studies have demonstrated that *TLE1* is overexpressed in synovial sarcomas and can be used as a diagnostic marker of synovial sarcoma [16-24]. However, Kosemehmetoglu et al. found that *TLE1* was not sufficiently specific for the diagnosis of synovial sarcoma [25].

Here, we investigated the expression of *TLE1* in genetically confirmed synovial sarcomas and nonsynovial sarcomas using tissue microarrays (TMAs) and evaluated the diagnostic value of *TLE1* for synovial sarcomas. Additionally, other traditional immunohistochemical markers were examined in this series of synovial sarcomas.

Materials and methods

Study cases and tumor specimens

This study was approved by the West China Hospital Institutional Review Board. Formalin-

fixed, paraffin-embedded (FFPE) tissue samples of soft tissue tumors were retrieved from the archives of the Department of Pathology of the West China Hospital of Sichuan University from January 2006 to June 2013. Pathology reports, histology sections, and immunohistochemically stained slides were reviewed by two experienced soft tissue pathologists (H.Z. and H.C.) and

3 general surgical pathologists (X.H., B.X., and T.Z.) according to the World Health Organization criteria [3]. A total of 387 cases were evaluated and included the following: 65 histologically diagnosed synovial sarcomas, 32 malignant peripheral nerve sheath tumors (MPNSTs), 46 solitary fibrous tumors (SFTs), 12 leiomyosarcomas, 8 myofibrosarcomas, 18 dermatofibrosarcoma protuberans (DFSP, 8 conventional, 10 fibrosarcomatous), 11 mesenchymal chondrosarcomas, 17 Ewing sarcomas, 18 rhabdomyosarcomas (5 alveolar, 13 embryonal), 10 fibrosarcomas, 10 myxofibrosarcomas, 15 epithelioid sarcomas, 14 clear cell sarcomas of the soft tissue, 11 hemangiopericytomas, 35 neurofibromas, 37 schwannomas (21 conventional, 16 cellular), 17 desmoid-type fibromatoses, and 11 spindle cell carcinomas.

FISH

All of the FFPE tissues from 65 histologically diagnosed synovial sarcomas were submitted to FISH. We used the commercially available Vysis LSI SS18 Dual Color Break Apart Probe (Abbott Molecular, Des Plaines, IL, USA) for SS18 on chromosome 18q11.2. The FISH analyses were performed on 4- μ m, paraffin-embedded thin tissue sections that were initially deparaffinized in xylene (2 \times 30 min), 100% ethanol (2 \times 5 min), 85% ethanol (5 min) and 70% ethanol (5 min) and treated with 10 mmol/l citric acid for 10 min in a humid microwave. The tissue sections were then transferred to 37°C sodium chloride-sodium citrate buffer (2 \times SSC) for 5 min, and the protein was digested with Digest All-3 (Zymed, San Francisco, CA, USA). After a brief wash in phosphate-buffered saline (1 \times PBS), the slides were sequentially dehydrated in ethanol (70%, 85% and 100%) and air-dried at room temperature. The tissue sections were denatured at 83°C for 5 min, and probe hybridization was performed overnight in a humidified chamber at 42°C. The tissue sec-

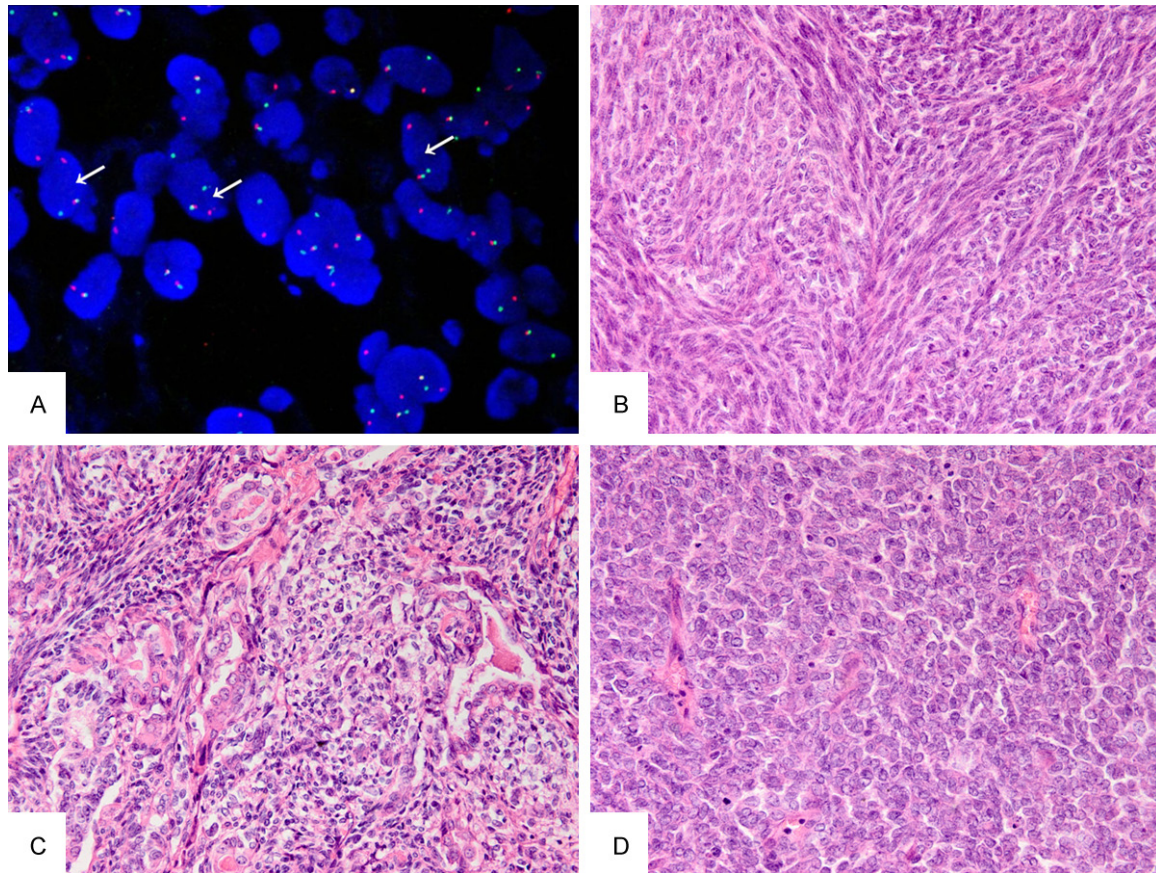


Figure 1. Histological types of genetically confirmed synovial sarcomas. A. Detection of SS18 rearrangement by FISH. The break-apart red and green signals indicated SS18 rearrangement (arrow; original magnification 1000×). B. Monophasic synovial sarcoma. C. Biphasic synovial sarcoma. D. Poorly differentiated synovial sarcoma (original magnification 400×).

tions were then washed in 0.3% NP40/2×SSC at 73°C for 2 min and subsequently washed in 0.1% NP40/2×SSC at room temperature for 2 min. The slides were then mounted in Vectashield mounting medium with 2.0 µg/ml of 4',6-diamidino-2-phenylindole (Abbott Molecular, Des Plaines, IL, USA). A split signal pattern was considered positive for the gene rearrangement if the distance between the green and red signals was greater than the diameter of either of the two signals. Cases were considered positive for rearrangement when 10% or more of the cells exhibited split signals [23]. Tumors were evaluated and scored by 2 independent investigators.

Construction of the TMA

To ensure that the synovial sarcomas were accurately diagnosed, only genetically positive cases were included in the TMA.

For each case, routinely hematoxylin and eosin stained sections were evaluated, and representative areas of the tissues were marked using a felt-tip pen for easy detection. One tissue cylinder with a diameter of 1.2 mm was punched from each morphologically representative area of each tissue block and placed in a recipient paraffin block (40 mm×30 mm×10 mm) using a homemade semiautomated tissue arrayer. To exclude bias due to possible tumor heterogeneity, 3 to 5 punches were taken from each of the tumor tissues.

Immunohistochemistry

Four-micrometer-thick sections were cut from the TMA blocks. Immunohistochemical studies of the synovial sarcomas were performed using the following antibodies: TLE1, EMA, cytokeratin (AE1/AE3), CK7, Bcl-2, and CD99 (Table 1). The other tumors were subjected only to TLE1

Table 2. TLE1 immunohistochemical staining of synovial sarcoma and other tumors

Tumor Type	n	3+	2+	1+	0	Total (%)
Synovial sarcoma	62	24	20	14	4	58 (94%)
MPNST	32	0	2	2	28	4 (13%)
SFT	46	1	1	6	38	8 (17%)
Leiomyosarcoma	12	0	0	1	11	1 (8%)
Myofibrosarcoma	8	0	0	1	7	1 (13%)
Conventional DFSP	8	0	0	0	8	0
Fibrosarcomatous DFSP	10	0	0	1	9	1 (10%)
Mesenchymal chondrosarcoma	11	0	0	0	11	0
Ewing sarcoma	17	0	0	0	17	0
Rhabdomyosarcoma	18	0	0	0	18	0
Fibrosarcoma	10	0	0	0	10	0
Myxofibrosarcoma	10	0	0	0	10	0
Epithelioid sarcoma	15	0	0	0	15	0
Clear cell sarcoma of soft tissue	14	0	0	0	14	0
Haemangiopericytoma	11	0	0	0	11	0
Neurofibroma	35	1	2	3	29	6 (17%)
Conventional schwannoma	21	1	3	2	15	6 (29%)
Cellular schwannoma	16	0	1	1	14	2 (13%)
Desmoid-type fibromatoses	17	0	0	1	16	1 (6%)
Spindle cell carcinoma	11	0	0	0	11	0

immunohistochemical staining. An EnVision detection system (Dako, Carpinteria, CA, USA) was utilized in the assessments of the aforementioned antibodies following standard procedures. 3,3'-diaminobenzidine (Dako, Carpinteria, CA, USA) was used as the chromogen, and the sections were counterstained with hematoxylin. Positive and negative control sections were utilized.

Regarding the TLE1 staining, only nuclear staining was recorded as positive staining. The results of the TLE1 immunohistochemical stainings were semi-quantitatively scored using a previously reported scoring system [16, 17]. The immunohistochemical staining was graded as 3+ (strong positive) if over 50% of the tumor cells exhibited intense nuclear staining as observed with a 4× objective lens; 2+ (moderately positive) if 26% to 50% of the tumor cells exhibited intense nuclear staining with a 4× objective lens or over 50% exhibited visible nuclear staining with a 10× objective lens; 1+ (weakly positive) if the tumor cells exhibited nuclear staining that was below the 2+ threshold; and 0 (negative) if no visible nuclear staining was present [16, 17].

Cytoplasmic stainings for AE1/AE3, CK7 and BCL-2 were considered positive, and membranous EMA staining was considered positive. Regarding CD99, cytoplasmic and cell membrane staining was considered positive staining. The results of these antibodies were evaluated according to the previous research [21].

Statistical analysis

An evaluation system of diagnostic and screening tests was used to assess the sensitivity and specificity of TLE1 expression for the diagnosis of synovial sarcoma. The chi-square test was utilized to compare the positive expression rates of TLE1 with those of the other immunohistochemical markers. *P*-values <0.05 were considered significant. The statistical analyses were performed using the Statistical Package for the Social Sciences 22.0 (IBM Corp., Armonk, NY, USA).

Results

Genetically confirmed synovial sarcomas

Sixty-five histologically diagnosed synovial sarcoma cases were verified by FISH, and the results revealed 62 positive cases (**Figure 1A**) and 3 failures. The main reason for failure was that the tissue sections escaped from the slide. To ensure that the cases of synovial sarcoma were accurately classified, the 62 genetically confirmed synovial sarcomas were ultimately included in this study.

The histological types of the 62 cases of synovial sarcomas included 46 monophasic, 7 biphasic, and 9 poorly differentiated tumors (**Figure 1B-D**).

TLE1 immunohistochemical staining results for the synovial sarcomas and other tumors

A summary of the TLE1 immunohistochemical staining results is provided in **Table 2**. The TLE1-positive expression rate in the synovial sarcomas was 94% (58/62), and 24 cases displayed 3+ staining (39%), 20 displayed 2+ staining (32%) and 14 displayed 1+ staining (23%) (**Figure 2**).

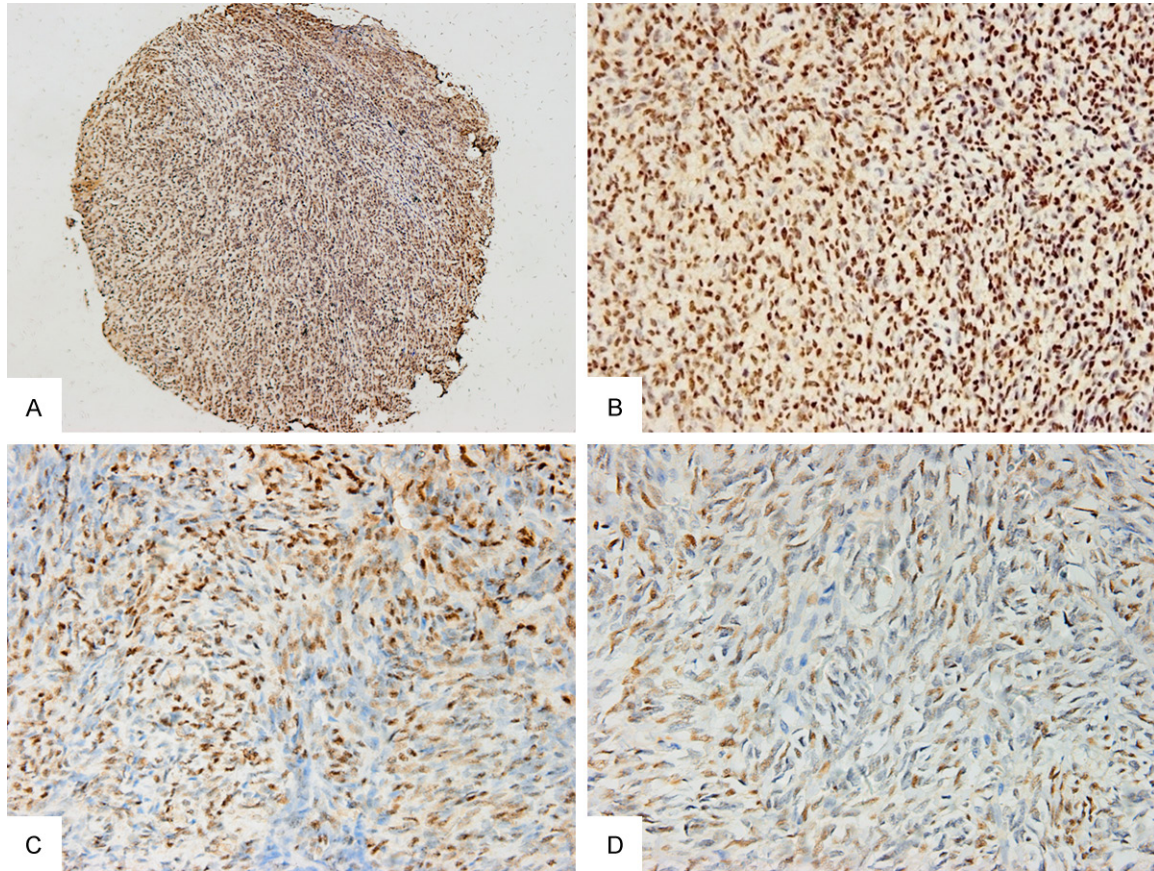


Figure 2. TLE1 immunohistochemical staining results in synovial sarcomas. A. Synovial sarcoma with 3+ TLE1 expression (original magnification 100×). B. Synovial sarcoma with 3+ TLE1 expression. C. Synovial sarcoma with 2+ TLE1 expression. D. Synovial sarcoma with 1+ TLE1 expression (original magnification 400×).

The rates of TLE1 positive expression in the monophasic, biphasic and poorly differentiated synovial sarcomas were 93% (43/46), 100% (7/7), and 89% (8/9), respectively. In the biphasic synovial sarcomas, TLE1 positivity was observed in both the spindle and epithelial cell components. There were no significant differences in the rates of TLE1 positivity between the different histologic types of synovial sarcomas ($\chi^2=0.807$, $P=0.668>0.05$).

In contrast, only 9% (30/322) of the nonsynovial sarcomas stained for TLE1 to various degrees. Three cases displayed 3+ staining (1%), including a SFT, a schwannoma, and a neurofibroma. Nine cases displayed 2+ staining (3%), including MNPSTs, schwannomas, neurofibromas and a SFT. Eighteen cases displayed 1+ staining (6%), including MPNSTs, SFTs, schwannomas, neurofibromas, a desmoid-type fibromatoses, a leiomyosarcoma, a myofibrosarcoma, and a fibrosarcomatous DF-

SP (**Figure 3**). The majority of the nonsynovial sarcomas (292/322, 91%), including conventional DFSPs, mesenchymal chondrosarcomas, Ewing sarcomas, rhabdomyosarcomas, fibrosarcomas, myxofibrosarcomas, epithelioid sarcomas, clear cell sarcomas of the soft tissue, haemangiopericytomas, and spindle cell carcinomas were completely negative for TLE1 (**Figure 4**).

Other immunohistochemical marker staining results in the synovial sarcomas

In the 62 synovial sarcoma cases (**Table 3**), EMA positivity was present in 54 (87%) cases, Bcl-2 positivity in 53 (85%), AE1/AE3 positivity in 38 (61%) and CK7 positivity in 22 (35%). These markers generally exhibited focal or patchy distribution patterns in the synovial sarcomas. The epithelial markers, including EMA, AE1/AE3 and CK7, were more pronounced in the epithelial component than in the spindled

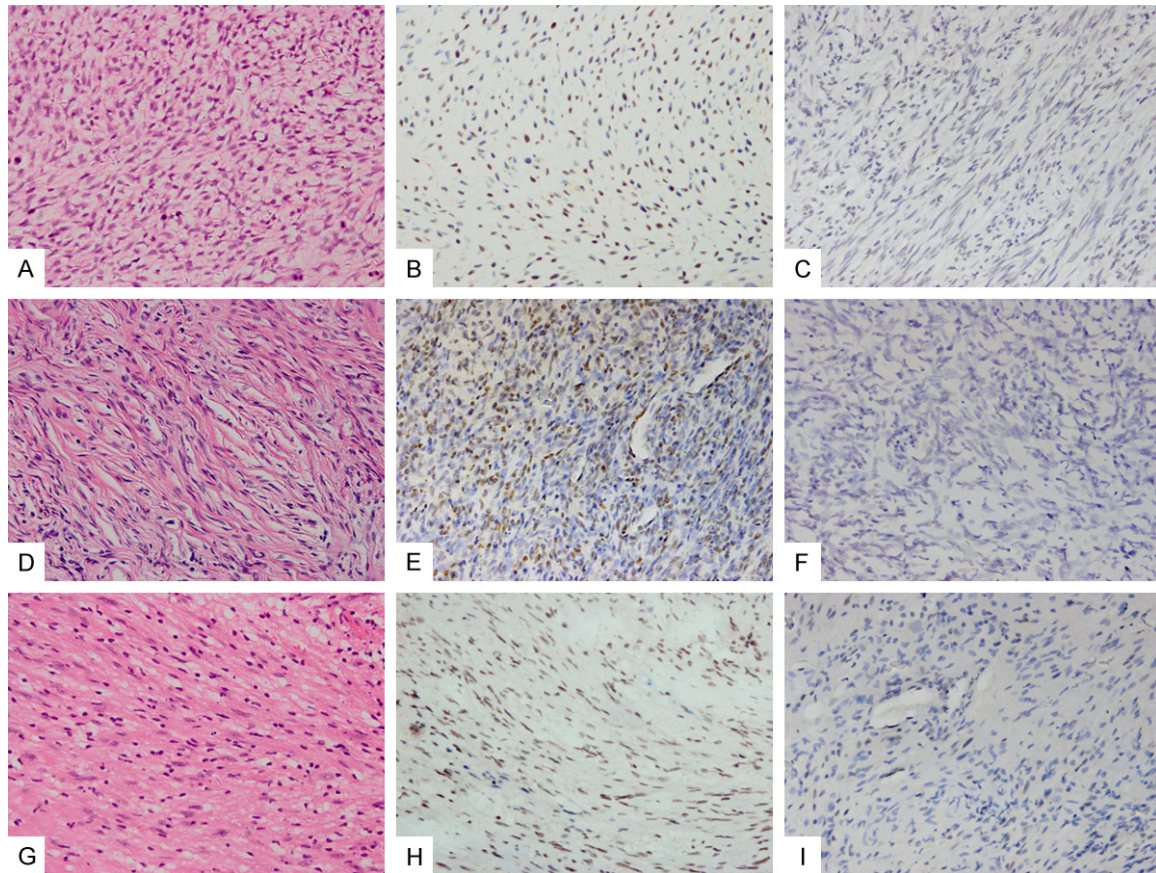


Figure 3. TLE1 immunohistochemical staining results for nonsynovial sarcomas. A. Myxoid area in a MPNST. B. MPNST with 2+ TLE1 expression. C. TLE1 negativity in a MPNSTs. D. Solitary fibrous tumor with a cracking artifact between the cells and collagen. E. Solitary fibrous tumor with 2+ TLE1 expression. F. TLE1 negativity in a SFT. G. Antoni B areas in a schwannoma. H. Schwannoma with 2+ TLE1 expression. I. TLE1 negativity in a schwannoma (original magnification 400×).

component. The rate of CD99 positive expression among the synovial sarcomas was only 24% (15/62), and the majority of these cases exhibited weak positivity in the cytoplasm (Figure 5).

Comparison of the immunohistochemical staining results for TLE1 and other markers in the synovial sarcomas

Among the 8 synovial sarcomas that were negative for EMA, all displayed TLE1 positivity. Among the 24 synovial sarcomas that were negative for AE1/AE3, 23 displayed TLE1 positivity. Among the 40 synovial sarcomas that were negative for CK7, 35 displayed TLE1 positivity. Among the 9 synovial sarcomas that were negative for Bcl-2, 8 displayed TLE1 positivity.

Among the 4 TLE1-negative cases (including 1 poorly differentiated and 3 monophasic synovi-

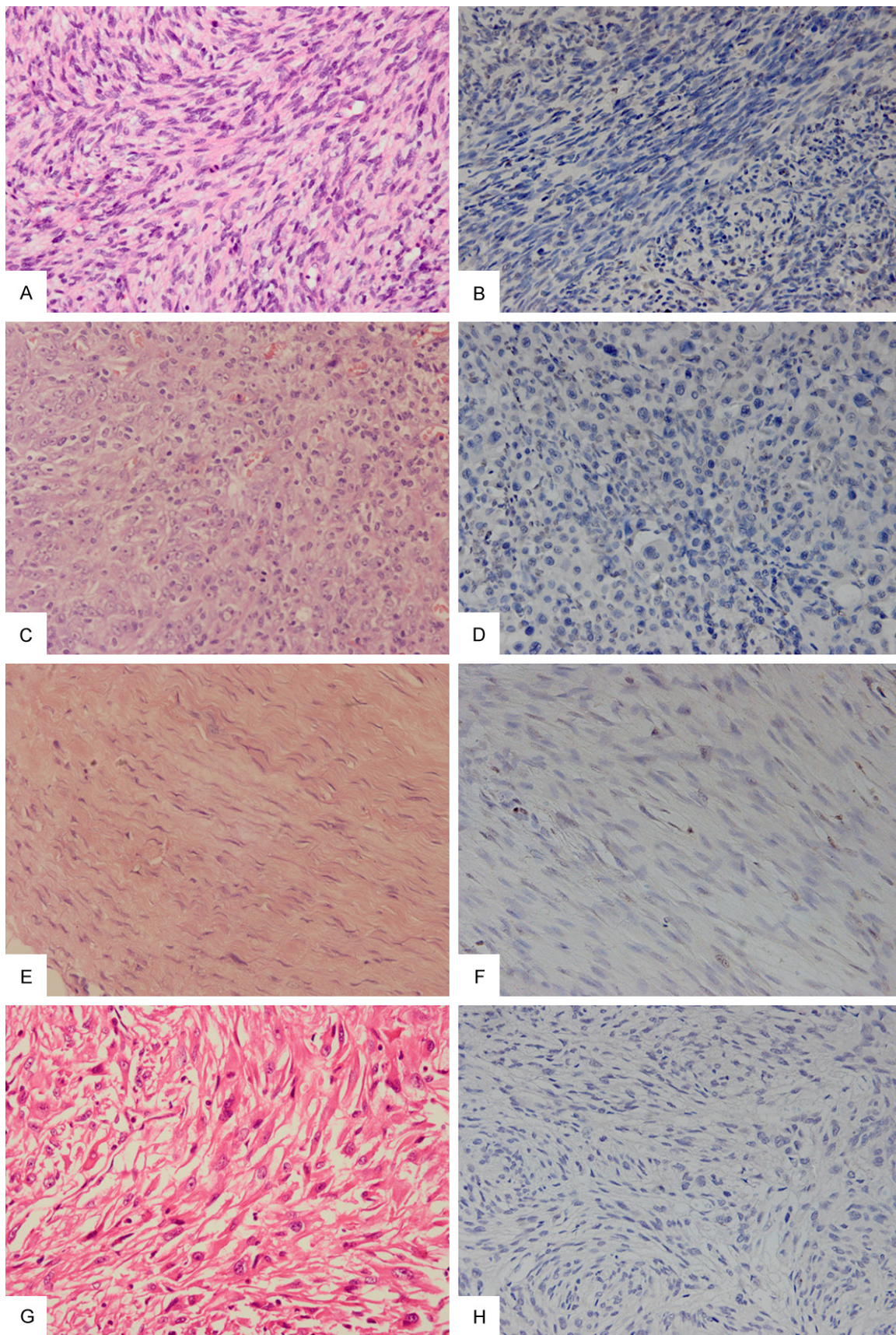
al sarcomas), 3 tumors exhibited at least focal positivities for epithelial markers (CKs and EMA) and Bcl-2.

Although the TLE1 positive rate was greater than those of EMA and Bcl-2, these differences were not significant (TLE1 vs. EMA: $\chi^2=1.476$, $P=0.224>0.05$; TLE1 vs. Bcl-2: $\chi^2=2.148$, $P=0.342>0.05$). The TLE1 positive rate was greater than those of AE1/AE3, CK7 and CD99, and these differences were significant (TLE1 vs. AE1/AE3: $\chi^2=18.452$, $P=0.000<0.05$; TLE1 vs. CK7: $\chi^2=45.655$, $P=0.000<0.05$; TLE1 vs. CD99: $\chi^2=61.584$, $P=0.000<0.05$).

Diagnostic values of TLE1 and other immunohistochemical markers for synovial sarcoma

Regarding the diagnosis of synovial sarcoma, the sensitivity and specificity of TLE1 staining were 94% and 91%, respectively. Accordingly,

TLE1 in synovial sarcomas



TLE1 in synovial sarcomas

Figure 4. TLE1 negativity in nonsynovial sarcomas. A. Fibrosarcomatous areas in a fibrosarcomatous DFSP. B. TLE1 negativity in a fibrosarcomatous DFSP. C. Malignant epithelioid cells in an epithelioid sarcoma. D. TLE1 negativity in an epithelioid sarcoma. E. A desmoid-type fibromatosis composed of spindle-shaped cells arranged in long fascicles. F. TLE1 negativity in a desmoid-type fibromatosis. G. Malignant spindle cells in a spindle cell carcinoma. H. TLE1 negativity in a spindle cell carcinoma (original magnification 400×).

Table 3. All immunohistochemical staining positive results in synovial sarcomas

Histologic Type	n	TLE1	EMA	Bcl-2	AE1/AE3	CK7	CD99
Monophasic	46	43 (93%)	41 (89%)	39 (85%)	28 (61%)	15 (33%)	12 (26%)
Biphasic	7	7 (100%)	7 (100%)	6 (86%)	6 (86%)	6 (86%)	2 (29%)
Poorly differentiated	9	8 (89%)	6 (67%)	8 (89%)	4 (44%)	1 (11%)	1 (11%)
Total	62	58 (94%)	54 (87%)	53 (85%)	38 (61%)	22 (35%)	15 (24%)

TLE1 displayed a positive predictive value of 66% and a negative predictive value of 99%.

EMA and Bcl-2 also exhibited high sensitivities (87% and 85%, respectively). In contrast, AE1/AE3, CK7 and CD99 displayed lower sensitivities (61%, 35% and 24%, respectively).

Discussion

Synovial sarcomas are sometimes difficult to distinguish from other nonsynovial sarcomas, especially when the tumors exhibit peculiar clinical findings or unusual morphologies. Traditionally, immunohistochemistry including epithelial marker has been used in the differential diagnosis of synovial sarcoma [5, 6]. Very recently, Terry et al. [16] first proposed TLE1 as a useful diagnostic marker for synovial sarcoma, and most subsequent studies have reported similar findings [17-24]. However, the diagnostic value of this biomarker remains controversial [25].

In the present study, we investigated the expression of TLE1 in genetically confirmed synovial sarcomas and nonsynovial sarcomas and compared the expression of TLE1 with traditional diagnostic markers in synovial sarcomas using TMAs. The results revealed that TLE1 positivity was observed in 94% (58/62) of the synovial sarcomas, with 94% sensitivity for the diagnosis of synovial sarcoma. Previous studies [16-24] have reported TLE1 sensitivities ranging from 73% to 100%.

The current study revealed that the sensitivity of TLE1 was greater than those of EMA, AE1/AE3, CK7, Bcl-2 and CD99, and these results are similar to those of some prior studies [17, 21]. However, it should be noted that the posi-

tive expression rates of EMA (87%), Bcl-2 (85%), AE1/AE3 (61%), CK7 (35%) and CD99 (24%) were slightly lower than those reported in previous studies [4, 17, 18, 21]. For example, Knösel T et al. [18] observed EMA positivity in 91% of synovial sarcomas, Bcl-2 positivity in 99.6%, PanCK (MNF) positivity in 73% and CK7 positivity in 96%. CD99 can be detected in 60% to 70% of synovial sarcomas [4]. The main reasons for the differences might be that we used TMAs instead of whole sections. The focal staining patterns of epithelial markers in synovial sarcomas are usually displayed in the epithelial component rather than the spindled component. Therefore, the positive rates of the epithelial markers may have been lower, to some degree, than those observed in conventional tissues. In contrast, TLE1 usually displays nuclear staining and a diffuse staining pattern in both the spindle and epithelial cell components, even in TMAs. Interestingly, the tissue volumes used in TMAs are very small and are thus similar to biopsy specimens to some extent. These findings imply that TLE1 is more sensitive and easier to interpret than traditional markers, especially in small biopsies. Rekhi B et al. [21] investigated TLE1 expression in 42 synovial sarcomas, including 8 biopsy specimens. In their study, authors suggested that TLE1 was a useful diagnostic marker for synovial sarcomas on small biopsy samples.

In our study, some synovial sarcomas did not express the traditional immunohistochemical markers but did exhibit TLE1 positivity. For example, one synovial sarcoma was negative for all of the traditional markers but displayed TLE1 2+ staining. Therefore, TLE1 is an excellent marker for the diagnosis of synovial sarcoma, especially in challenging cases.

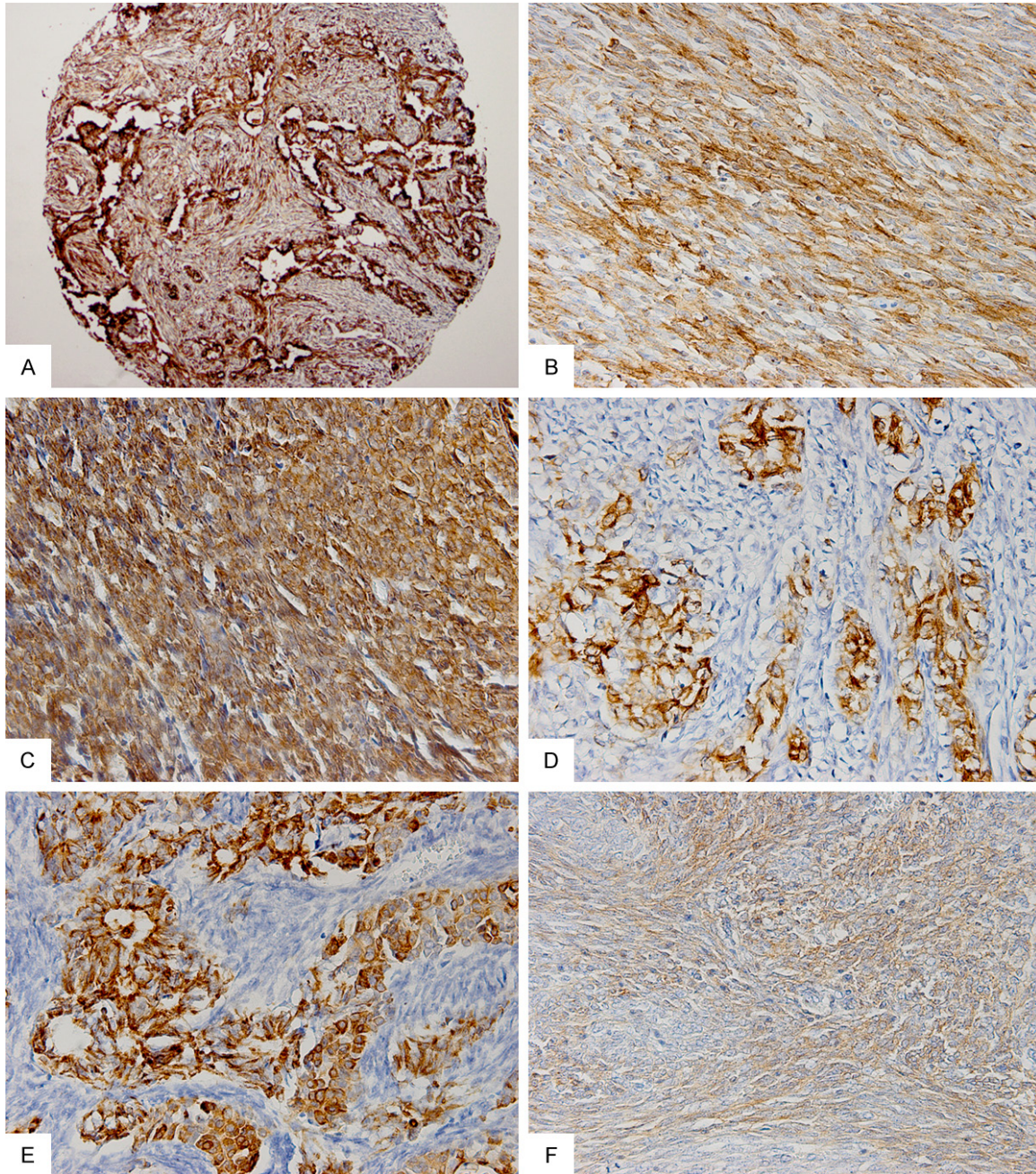


Figure 5. Other immunohistochemical marker staining results for synovial sarcomas. A. Positive expression of EMA in a biphasic synovial sarcoma (original magnification 100×). B. Positive expression of EMA in a monophasic synovial sarcoma. C. Positive expression of Bcl-2 in a synovial sarcoma. D. Focal staining for AE1/AE3 in a monophasic synovial sarcoma. E. Positive expression of CK7 in the epithelial component of a biphasic synovial sarcoma. F. Weakly positive expression of CD99 in a synovial sarcoma (original magnification 400×).

We also observed 4 synovial sarcoma cases that were negative for TLE1 but displayed positivity for at least one of traditional antibodies. Therefore, TLE1 and traditional immunohistochemical markers may be complementary in the diagnosis of synovial sarcoma. Notably, molecular testing should be considered for extremely difficult cases.

In the present study, 9% (30/322) of the nonsynovial sarcomas exhibited reactivity for TLE1 to varying degrees. Notably, only 4% (12/322) of these tumors exhibited 2+ or 3+ staining, including MNPSTs, SFTs, schwannomas and neurofibromas. Generally, our results indicated that TLE1 was highly specific for synovial sarcomas and not nonsynovial sarcomas, which is

similar to the results of most previous studies [16, 18, 19, 22]. However, in the study by Kosemehmetoglu et al [25], TLE1 expression was detected in 37% (53/143) of nonsynovial sarcomas, and 36 of these cases (25%) exhibited 2+ or 3+ staining, which suggests that TLE1 is not so specific. Some authors have indicated that such discrepant results may arise from the use of different methods of antigen retrieval, different immunohistochemical detection systems, or different scoring systems for this marker [17, 22]. Of course, further investigation is warranted to answer this question.

In this study, 4% (2/46) of the SFTs and 6% (2/32) of the MPNSTs exhibited 2+ or 3+ TLE1 staining, which constituted the main differential diagnosis of synovial sarcoma. Synovial sarcomas can exhibit hemangiopericytoma-like patterns that are histologically similar to SFTs, but SFTs typically exhibit diffuse CD34 staining, and synovial sarcomas are virtually always negative for CD34 [4]. MPNST seems to be the most challenging tumor type in the differential diagnosis of synovial sarcomas in any location. MPNSTs can closely resemble synovial sarcomas (especially the monophasic type) not only histologically but also immunohistochemically. Both synovial sarcomas and MPNSTs can exhibit hemangiopericytoma-like patterns. Additionally, 30% of synovial sarcomas exhibit focal immunoreactivity for the S-100 protein, whereas approximately two-thirds of MPNSTs focally express the S-100 protein [4]. Moreover, some MPNSTs can also express epithelial markers [26], and focal positivities for these markers are typical features of synovial sarcomas [4]. In such situations, the definitive diagnosis should be aided by molecular tests for t(X;18). In our study, 2 cases of MPNSTs exhibited 2+ TLE1 staining; to confirm the diagnoses, we used FISH to detect t(X;18) and observed negative results.

Our study and the majority of the previous studies have demonstrated TLE1 overexpression in the majority of synovial sarcomas. Furthermore, Seo et al. [15] found that TLE1 is a critical factor for the survival of synovial sarcoma cells and that normal cells with mesenchymal origins never express TLE1; thus, TLE1 may be a potential therapeutic target for synovial sarcomas. As is well known, Bcl-2 is an anti-apoptot-

ic protein that is overexpressed in the vast majority of synovial sarcomas. Using western blot analysis, Seo et al. found that the expression of Bcl-2 in synovial sarcomas is suppressed by TLE1 knock-down, which suggests that TLE1 regulates Bcl-2 expression [15]. In vivo studies of synovial sarcoma cell lines have demonstrated that Bcl-2 (G3139) antisense oligonucleotides decrease Bcl-2 expression, induce apoptosis and enhance doxorubicin cytotoxicity [27]. Therefore, detecting the expression of TLE1 may guide the treatment of synovial sarcomas in the future.

In summary, this study is the first single-center, large-scale analysis of TLE1 immunohistochemical staining in synovial sarcomas and other soft tissue tumors in Chinese patients. TLE1 is highly sensitive for synovial sarcomas and more sensitive than traditional immunohistochemical markers. Additionally, this marker is also very specific as demonstrated by the observation that only a very small subset of nonsynovial sarcomas, including MPNSTs and SFTs, can exhibit TLE1 positivity. This antibody can be used as a useful screening marker for synovial sarcomas, although complementary molecular studies remain the gold standards for the diagnosis of entity.

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Disclosure of conflict of interest

None.

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TLE1 in synovial sarcomas

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