Impact of SAMHD1 and phosphorylated ATM levels on the progression and prognosis of patients with soft tissue sarcoma

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Abstract. Soft tissue sarcomas (STSs) are rare and heterogeneous malignancies that are often associated with a poor prognosis, particularly in advanced stages. DNA damage repair (DDR) pathways serve a crucial role in cancer progression and response to treatment. Among the key regulators of DDR are SAM domain and HD domain-containing protein 1 (SAMHD1) and phosphorylated ataxia-telangiectasia mutated (p-ATM), both of which contribute to maintaining genomic stability. However, to the best of our knowledge, their clinical significance in STS has not been fully elucidated. In the present study, immunohistochemistry was used to assess the levels of SAMHD1 and p-ATM in tumor tissues. The prognostic impact of SAMHD1 and p-ATM levels was evaluated through survival analysis. The results showed that high levels of SAMHD1 and p-ATM were significantly associated with worse overall survival and progression-free survival. Multivariate Cox analysis demonstrated that both SAMHD1 and p-ATM levels were independent predictors of poor prognosis. Notably, patients exhibiting co-expression of SAMHD1 and p-ATM experienced the poorest clinical outcomes, suggesting a synergistic effect in promoting sarcoma progression. These findings indicated that SAMHD1 and p-ATM may serve as valuable prognostic biomarkers in STS. Their involvement in DDR mechanisms also highlights their potential as novel therapeutic targets, especially for patients with aggressive or high-risk disease profiles.

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Introduction

Sarcomas are uncommon malignancies, accounting for approximately 1% of adult cancers and 15% of pediatric cancers (1). Sarcomas are not only uncommon, but also vary in their locations, features, and subtypes; there are more than 100 distinct soft tissue sarcoma (STS) subtypes that have been classified so far (2,3). Due to these complexities, STS presents significant diagnostic challenges and the prognosis remains poor despite advancements in treatment like radiation therapy and chemotherapy. Between 2000 and 2018, the 5-year survival rate for STS with distant metastasis was only 16.7% (4). Therefore, it is essential to explore novel therapeutic approaches for treatment of STS patients.

Recent studies have highlighted the crucial role of DNA damage repair (DDR) pathways in both cancer development and treatment (5-8). DDR contributes to the maintenance of genomic stability by repairing DNA damage, and its dysfunction can lead to oncogenesis, ultimately promoting the development of cancer (5). Moreover, therapies such as chemotherapy and radiotherapy induce DNA damage to eliminate cancer cells, with tumors harboring mutations in DNA repair genes often displaying increased sensitivity to such treatments due to their reduced DNA repair efficiency (6). SAMHD1 and p-ATM are key regulators of the DDR pathway (9-12). Their roles in DNA repair and their potential as therapeutic targets in cancer warrant further investigation.

SAMHD1 is primarily known for its role as a deoxynucleoside triphosphate triphosphohydrolase (dNTPase), preventing abnormal DNA re-synthesis during the DNA end-joining process (10). When SAMHD1 function is impaired, this process is disrupted, leading to genomic instability, which

ultimately contributes to cancer development (11). One cancer type associated with this mechanism is chronic lymphocytic leukemia (CLL) (11). Research on the impact of SAMHD1 expression on cancer prognosis is ongoing across various cancers (13-16). In colorectal cancer, patients with decreased SAMHD1 expression have been shown to have a poor prognosis, which is hypothesized to be due to the dNTPase activity, which inhibits tumor cell proliferation and promotes apoptosis (13). Conversely, a recent study in breast cancer reported that tumors expressing SAMHD1 exhibited shorter progression-free and overall survival following chemotherapy (14). This study suggested that SAMHD1 depletion reduced interleukin signaling, potentially altering immune cell infiltration (14).

ATM is essential for the repair of DNA double-strand breaks, regulating cell cycle checkpoints, and triggering apoptosis (9,17). Upon DNA damage, ATM is recruited to the site of damage and is activated through autophosphorylation, forming p-ATM, which subsequently preserves genomic integrity by regulating various cellular processes (18). ATM has long been recognized as a key tumor suppressor in the context of tumorigenesis (19,20). However, several studies have revealed that ATM signaling paradoxically supports tumor progression in certain biological settings, indicating a more complex and context-dependent role in cancer development. Several studies have provided evidence supporting the oncogenic role of ATM in cancer progression, as outlined below. In melanoma patients, both high expression and loss of p-ATM have been identified as markers of poor survival (21). This is likely because overactivation of p-ATM-related signaling pathways also promotes tumorigenesis, while the loss of p-ATM undermines genome maintenance, leading to cancer progression (21,22). In pancreatic cancer, decreased p-ATM expression has been linked not only to poor prognosis but also to the upregulation of anti-apoptotic genes such as BCL-2/BAD, contributing to gemcitabine resistance (17).

Several studies have demonstrated that the DDR activity of SAMHD1 is dependent on ATM-mediated signaling, either through direct phosphorylation or indirect modulation of its stability and recruitment (23-25). Conversely, loss of SAMHD1 has been associated with aberrant ATM pathway activation, leading to increased genomic instability and tumorigenesis (26). Collectively, these findings suggest a functional interplay between SAMHD1 and p-ATM, particularly in the context of genome integrity under replicative stress or genotoxic insult (23-26).

Despite increasing interest in the role of DDR components in cancer biology, the clinical significance of SAMHD1 and p-ATM expression in STS remains poorly characterized. To date, no comprehensive studies have evaluated the prognostic or pathological implications of SAMHD1 and p-ATM expression specifically in STS. Given their pivotal roles in genome maintenance and the emerging evidence of their functional interaction in the DDR network, investigating the expression patterns of SAMHD1 and p-ATM in STS might provide valuable insights into tumor behavior and patient outcomes. Therefore, in this study, we evaluated the expression of SAMHD1 and p-ATM in STS tissues and assessed their associations with clinicopathological parameters and patient prognosis.

Materials and methods

Ethical approval. This study received approval from the Institutional Review Board of Jeonbuk National University Hospital (IRB number: 2024-04-026-001) and was conducted in compliance with the Declaration of Helsinki. The requirement for written informed consent was waived by the IRB due to the retrospective nature of the study and the use of anonymized data.

Patients and samples. A total of 133 patients with STS were included in this study. The patient selection was based on the following inclusion criteria: i) Patients histopathologically diagnosed with STS; ii) patients who underwent surgical resection at Jeonbuk National University Hospital between January 2000 and November 2022; iii) availability of formalin-fixed paraffin-embedded (FFPE) tissue blocks suitable for tissue microarray (TMA) construction; and iv) availability of complete clinicopathological and follow-up data from medical records. The exclusion criteria were: i) Cases with insufficient or poor-quality tissue material for TMA analysis; and ii) patients with incomplete clinical data or those lost to follow-up.

Histological types of STS included in this study are listed in Table I. Clinicopathologic information was obtained by reviewing medical records. Factors included sex, age, site, T category, lymph node metastasis, M category, histologic grade, tumor differentiation, mitotic count, and tumor necrosis. Histologic slides were reviewed according to the WHO classification of tumors of soft tissue and bone tumor (27) and graded using the FNCLCC (French Fédération Nationale des Centres de Lutte Contre le Cancer) grading system (28). T category and M category were classified with reference to the 8th edition of the American Joint Committee Cancer Staging System (29).

Immunohistochemical staining and scoring. We constructed a TMA using paraffin-embedded tissue blocks obtained from surgical specimens of 133 STS patients. Two cores, each 3.0 mm in size, were collected from non-necrotic, non-degenerative areas of tumors. TMA tissue sections were deparaffinized, followed by antigen retrieval performed in pH 6.0 antigen retrieval solution (DAKO, Glostrup, Denmark) using a microwave oven for 20 min. Primary antibodies for SAMHD1 (1:50, PA5-21515, Invitrogen, Waltham, MA) and p-ATM (1:50, sc-47739, Santa Cruz Biotechnology, Santa Cruz, CA) were incubated with the TMA tissue section overnight at 4˚C.

Two pathologists (KMK and YJK) who were blinded to the clinicopathologic information of the patients assessed immunohistochemical staining under a multi-view microscope (Nikon Eclipse 80i; Nikon, Tokyo, Japan) by consensus. Both SAMHD1 and p-ATM were expressed mostly in nuclei (Fig. 1). As previous studies on the immunohistochemical expression of SAMHD1 and p-ATM have primarily focused on nuclear staining patterns, our analysis was likewise based on nuclear localization (13,14,17,21). To evaluate staining, we first identified the region with the highest density of positive cells under low magnification and then counted positive cells per high-power field (HPF), with a maximum of 50 cells per field. Finally, we calculated the average by summing the counts

Table I. Expression status of SAMHD1 and p-ATM according to the histological type of soft tissue sarcoma.

		SAMHD1 expression		p-ATM expression	
Histological type	No.	Positive, n (%)	P-value	Positive, n (%)	P-value
Leiomyosarcoma	23	16 (69.6)	0.011	12 (52.2)	0.368
Synovial sarcoma	20	9 (45.0)	>0.999	12 (60.0)	0.143
Undifferentiated sarcoma	15	10 (66.7)	0.096	10 (66.7)	0.095
Myxoid liposarcoma	13	3 (23.1)	0.144	1 (7.7)	0.007
Myxofibrosarcoma	8	3 (37.5)	>0.999	0 (0.0)	0.010
Well-differentiated liposarcoma	8	2 (25.0)	0.300	2 (25.0)	0.465
Angiosarcoma	7	3 (42.9)	>0.999	5 (71.4)	0.239
Malignant peripheral nerve sheath tumor	6	5 (83.3)	0.088	3 (50.0)	>0.999
Ewing sarcoma	6	2 (33.3)	0.693	3 (50.0)	>0.999
Adult fibrosarcoma	6	2 (33.3)	0.693	3 (50.0)	>0.999
Low-grade myofibroblastic sarcoma	5	0 (0.0)	0.066	0 (0.0)	0.068
Alveolar rhabdomyosarcoma	4	3 (75.0)	0.322	3 (75.0)	0.317
Dedifferentiated liposarcoma	3	1 (33.3)	>0.999	1 (33.3)	>0.999
Embryonal rhabdomyosarcoma	2	0 (0.0)	0.503	0 (0.0)	0.504
Pleomorphic rhabdomyosarcoma	2	0 (0.0)	0.503	1 (50.0)	>0.999
Epithelioid sarcoma	2	0 (0.0)	0.503	1 (50.0)	>0.999
Pleomorphic liposarcoma	1	0 (0.0)	>0.999	0 (0.0)	>0.999
Spindle cell rhabdomyosarcoma	1	0 (0.0)	>0.999	0 (0.0)	>0.999
Extraskeletal myxoid chondrosarcoma	1	0 (0.0)	>0.999	1 (100.0)	0.436

P-values were calculated using Fisher's exact test based on 2x2 contingency tables, in which each histological subtype was compared with all other subtypes combined, stratified by positive vs. negative expression of the marker. p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

from each TMA section. The diameter of HPF was 625 μm. and the area of one HPF was 306,796 μm^2.

Statistical analysis. Patients were categorized into positive and negative subgroups based on the immunohistochemical expression levels of SAMHD1 and p-ATM. Cutoff values for both markers to identify the threshold with the highest prognostic accuracy for predicting patient death were established through receiver operating characteristic (ROC) curve analysis. The end date of follow-up was either the date of patient death or the last contact date by December 2022. Prognostic outcomes were evaluated by calculating overall survival (OS) and progression-free survival (PFS). In the OS analysis, death specifically due to STS was considered an event, while cases where patients were alive at their last follow-up or died from other causes were censored. In the PFS analysis, relapse and metastasis of STS and death due to STS were treated as events. Statistical analysis was conducted using SPSS software (IBM, version 26.0, Armonk, NY). To evaluate differences in SAMHD1 and p-ATM expression among histological subtypes, Fisher's exact test was performed for pairwise comparisons between each subtype and the remainder of the cohort. Kaplan-Meier survival analysis with the log-rank test was used to compare survival distributions between groups. For pairwise comparisons between subgroups, P-values were obtained using the log-rank test and adjusted for multiple testing using Bonferroni's correction. Cox proportional hazards regression was used to evaluate the prognosis of STS. Stepwise selection was employed to include variables independently associated with survival in the multivariate Cox model. Pearson's chi-square test assessed the associations between immunohistochemical expression and clinicopathological factors, while the correlation between SAMHD1 and p-ATM expression was determined using Pearson's and Spearman's correlation tests. P-values less than 0.05 were considered statistically significant.

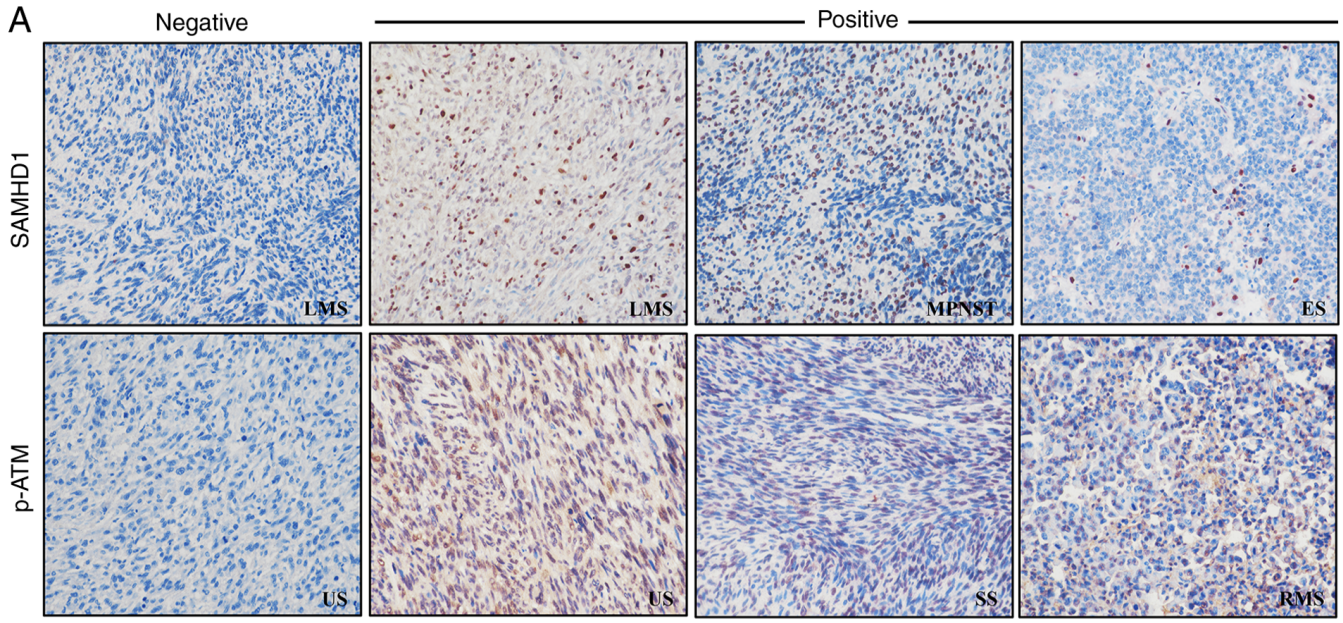
Table II. Association between SAMHD1 and p-ATM levels.

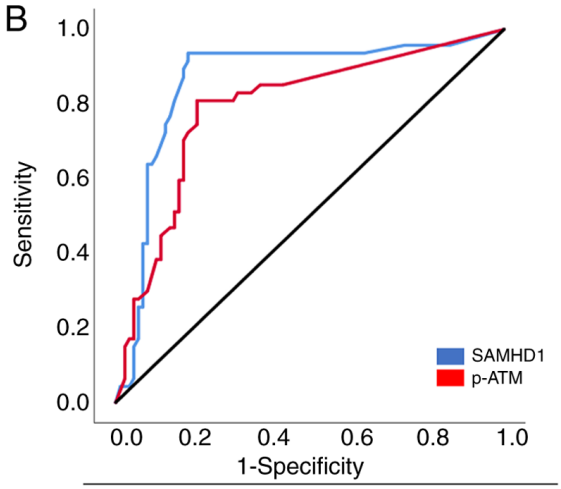
	SAMHD1 expression		
p-ATM expression	Positive, n (%)	Negative, n (%)	P-value
Positive	47 (82.5)	10 (17.5)	
Negative	13 (17.1)	63 (82.9)	<0.001

p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

Results

Expression of SAMHD1 and p-ATM in STS tissues. Fig. 1 shows the immunohistochemical staining patterns of SAMHD1 and





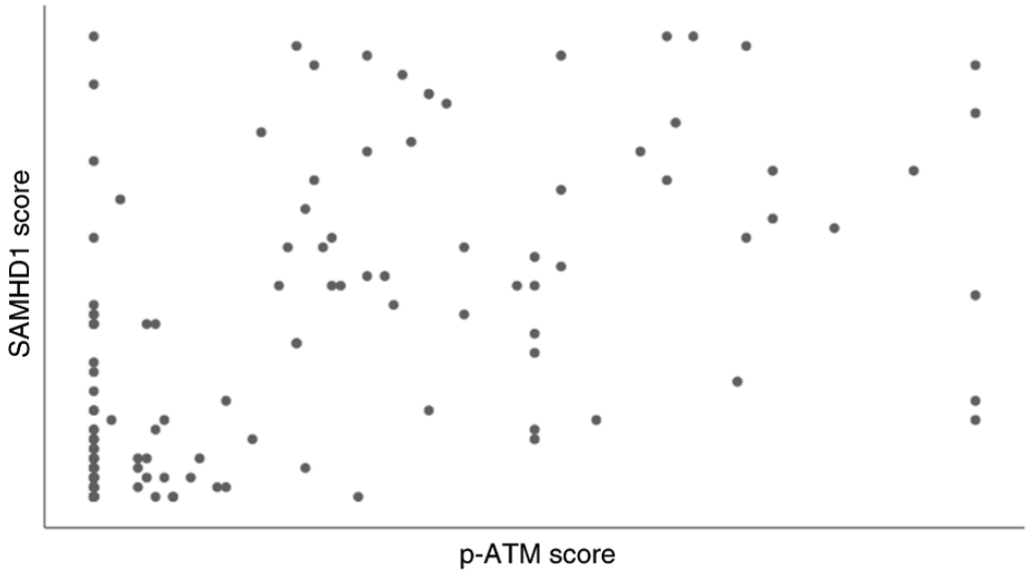
Variable	Cut-off	AUC	P-value
SAMHD1	≥10/HPF	0.847	<0.001
p-ATM	≥9/HPF	0.791	<0.001

Figure 1. (A) Immunohistochemistry of SAMHD1 and p-ATM in various STSs (original magnification, x400). (B) Receiver operating characteristic curve analysis to determine cut-off points for the levels of nuclear SAMHD1 (blue line) and nuclear p-ATM (red line). The cut-off points indicate the point of the highest AUC to predict the death of patients with STS. AUC, area under the curve; ES, Ewing sarcoma; HPF, high-power field; LMS, leiomyosarcoma; MPNST, malignant peripheral nerve sheath tumor; p-ATM, phosphorylated ataxia-telangiectasia mutated; RMS, rhabdomyosarcoma; SAMHD1, SAM domain and HD domain-containing protein 1; SS, synovial sarcoma; STS, soft tissue sarcoma; US, undifferentiated sarcoma.

p-ATM in STS tissue samples; both these markers exhibited predominantly nuclear expression (Fig. 1A). ROC curve analysis, using patient death as a determinant, was employed to segregate individuals into SAMHD1- and p-ATM-positive and negative groups. Optimal cutoff values were defined as 10/HPF for SAMHD1 and 9/HPF for p-ATM (Fig. 1B). Positivity rates of SAMHD1 and p-ATM across various histologic types of STS are summarized in Table I.

Correlation between SAMHD1 and p-ATM expression. Based on previous reports indicating a functional interaction between SAMHD1 and p-ATM in the DDR pathway, we analyzed a relationship between their immunohistochemical expression. Chi-square tests revealed a significant correlation between SAMHD1 and p-ATM expression when comparing positive and negative expression groups (P<0.001) (Table II). Furthermore, Pearson's correlation analysis showed a moderate correlation (r=0.520, P<0.001), and Spearman's correlation revealed a stronger association (r=0.607, P<0.001) between the immunohistochemical staining scores of SAMHD1 and p-ATM (Fig. 2).

Associations of individual and combined patterns of SAMHD1 and p-ATM expression with clinicopathological factors. Individual SAMHD1 positivity was associated with higher histologic grade (P=0.018) (Table III). p-ATM positivity showed strong correlations with T category (P=0.005) and histologic grade (P=0.001) (Table III).



Correlation test	r	P-value
Pearson's correlation coefficient	0.520	<0.001
Spearman's correlation coefficient	0.607	<0.001

Figure 2. Scattergram comparing immunohistochemical scores of SAMHD1 and p-ATM levels in soft tissue sarcoma. Immunohistochemical scores of SAMHD1 and p-ATM exhibited a significant positive correlation. p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

Additionally, we reclassified patients into three sub-groups based on SAMHD1 and p-ATM expression levels: SAMHD1+/p-ATM+, SAMHD1+/p-ATM- or SAMHD1-/p-ATM+, and SAMHD1-/p-ATM-. Co-expression of SAMHD1 and p-ATM was significantly associated with histologic grade (P=0.003) (Table III).

Univariate and Kaplan-Meier survival analyses of individual and combined expression patterns of SAMHD1 and p-ATM for OS and PFS of STS patients. Analysis of various clinical parameters using univariate methods showed significant correlations between several factors and patient outcomes. Specifically, T category (P=0.005), M category (P=0.038) and histologic grade (P=0.013) were significantly associated with poor OS, along with SAMHD1 expression (P<0.001), p-ATM expression (P<0.001), and co-expression pattern of SAMHD1 and p-ATM (P<0.001) (Table IV). In univariate analysis of PFS, age (P=0.016), M category (P<0.001) and histologic grade (P=0.007) were significantly associated with shorter PFS. SAMHD1 (P<0.001), p-ATM (P=0.001), and co-expression of SAMHD1 and p-ATM (P<0.001) also showed correlations with shorter PFS in the univariate analysis (Table IV).

Patients with positive SAMHD1 expression faced a 7.583-fold higher risk of death [95% confidential interval (CI) 3.536-16.262, P<0.001)], as well as a 4.621-fold greater risk of disease progression or mortality (95% CI; 2.805-7.614, P<0.001). Patients positive for p-ATM expression exhibited a 7.65-fold (95% CI; 3.688-15.87, P<0.001) elevated risk of death and a 2.939-fold higher risk of disease progression or mortality (95% CI; 1.853-4.661, P<0.001) compared to those with negative expression (Table IV). Regarding the co-expression of SAMHD1 and p-ATM, STS patients who were SAMHD1+/p-ATM- or SAMHD1-/p-ATM+ had a 7.179-fold (95% CI; 2.001-25.753) and a 3.694-fold (95% CI; 1.926-7.085) increased risk of death and progression or death, respectively, compared to STS patients with the SAMHD1-/p-ATM-expression pattern. STS patients with the SAMHD1+/p-ATM+ expression pattern exhibited even higher risks, with a 22.774-fold (95% CI; 6.95-74.624) and a 6.213-fold (95% CI; 3.387-11.398) increased likelihood of death and relapse or death, respectively, compared to STS patients with the SAMHD1-/p-ATM-expression pattern (Table IV). Kaplan-Meier survival curves for OS and PFS based on individual and co-expression patterns of SAMHD1 and p-ATM in STS patients are presented in Fig. 3.

Multivariate survival analysis of individual and combined expression patterns of SAMHD1 and p-ATM for OS and PFS of STS patients. To investigate the impact of individual and combined expression of SAMHD1 and p-ATM on OS and PFS in STS patients, we performed multivariate survival analyses. Expression patterns were independently analyzed using two models: Model 1 for individual expression and Model 2 for co-expression. Each model included the expression pattern along with other clinicopathological variables that were statistically significant for OS or PFS in the univariate analysis.

Table III. Clinicopathologic variables and levels of SAMHD1 and p-ATM in soft tissue sarcoma.

		SAMHD1 expression			p-ATM expression			Combined expression			
Characteristics	Total, n	Positive, n (%)	Negative, n (%)	P-value	Positive, n (%)	Negative, n (%)	P-value	SAMHD1$^+$/ p-ATM$^+$, n (%)	SAMHD1$^+$/p-ATM$^-$ or SAMHD$^-$/ p-ATM$^+$, n (%)	SAMHD1$^-$/ p-ATM$^-$, n (%)	P-value
All cases	133	59 (44.4)	74 (55.6)		57 (42.9)	76 (57.1)		42 (31.6)	32 (24.1)	59 (44.4)	
Sex											
Male	74	32 (43.2)	42 (56.8)		28 (37.8)	46 (62.2)		22 (29.7)	16 (21.6)	36 (48.6)	
Female	59	27 (45.8)	32 (54.2)	0.771	29 (49.2)	30 (50.8)	0.190	20 (33.9)	16 (27.1)	23 (39.0)	0.526
Age, years											
≤60	76	34 (44.7)	42 (55.3)		34 (44.7)	42 (55.3)		25 (32.9)	18 (23.7)	33 (43.4)	
>60	57	25 (43.9)	32 (56.1)	0.920	23 (40.4)	34 (59.6)	0.613	17 (29.8)	14 (24.6)	26 (45.6)	0.931
Site											
Head and neck	9	4 (44.4)	5 (55.6)		5 (55.6)	4 (44.4)		3 (33.3)	3 (33.3)	3 (33.3)	
Trunk and extremities	105	44 (41.9)	61 (58.1)		43 (41.0)	62 (59.0)		32 (30.5)	23 (21.9)	50 (47.6)	
Abdomen and thoracic visceral organs	15	10 (66.7)	5 (33.3)		8 (53.3)	7 (46.7)		7 (46.7)	4 (26.7)	4 (26.7)	
Retroperitoneum	4	1 (25.0)	3 (75.0)	0.274[a]	1 (25.0)	3 (75.0)	0.585[a]	0 (0.0)	2 (50.0)	2 (50.0)	0.321[a]
T category											
T 1, 2	94	39 (41.5)	55 (58.5)		33 (35.1)	61 (64.9)		25 (26.6)	22 (23.4)	47 (50.0)	
T 3, 4	39	20 (51.3)	19 (48.7)	0.301	24 (61.5)	15 (38.5)	0.005	17 (43.6)	10 (25.6)	12 (30.8)	0.087
LN metastasis											
Absent	120	52 (43.3)	68 (56.7)		48 (40.0)	72 (60.0)		38 (31.7)	27 (22.5)	55 (45.8)	
Present	13	7 (53.8)	6 (46.2)	0.562[a]	6 (46.2)	7 (53.8)	0.769[a]	4 (30.8)	5 (38.5)	4 (30.8)	0.398[a]
M category											
M0	123	53 (43.1)	70 (56.9)		50 (40.7)	73 (59.3)		37 (30.1)	29 (23.6)	57 (46.3)	
M1	10	6 (60.0)	4 (40.0)	0.338[a]	7 (70.0)	3 (30.0)	0.098[a]	5 (50.0)	3 (30.0)	2 (20.0)	0.251[a]
Histologic grade											
Grade 1	31	8 (25.8)	23 (74.2)		5 (16.1)	26 (83.9)		4 (12.9)	5 (16.1)	22 (71.0)	
Grade 2 and 3	102	51 (50.0)	51 (50.0)	0.018	50 (49.0)	52 (51.0)	0.001	38 (37.3)	27 (26.5)	37 (36.3)	0.003
Tumor differentiation											
1	16	8 (50.0)	8 (50.0)		7 (43.8)	9 (56.3)		6 (37.5)	3 (18.8)	7 (43.8)	
2 and 3	117	51 (43.6)	66 (56.4)	0.789[a]	50 (42.7)	67 (57.3)	>0.999[a]	36 (30.8)	29 (24.8)	52 (44.4)	0.812[a]
Mitotic count											
0-9/10 HPF	62	27 (43.5)	35 (56.5)		24 (38.7)	38 (61.3)		17 (27.4)	17 (27.4)	28 (45.2)	
≥10/10 HPF	71	32 (45.1)	39 (54.9)	0.860	33 (46.5)	38 (53.5)	0.366	25 (35.2)	15 (21.1)	31 (43.7)	0.549

Table III. Continued.

Characteristics	Total, n	SAMHD1 expression			p-ATM expression			Combined expression			
		Positive, n (%)	Negative, n (%)	P-value	Positive, n (%)	Negative, n (%)	P-value	SAMHD1$^+$, p-ATM$^+$, n (%)	SAMHD1$^+$/p-ATM$^-$ or SAMHD1$^-$/ p-ATM$^+$, n (%)	SAMHD1$^-$/ p-ATM$^-$, n (%)	P-value
Tumor necrosis											
Absent	71	28 (39.4)	43 (60.6)		25 (35.2)	46 (64.8)		17 (23.9)	19 (26.8)	35 (49.3)	
Present	62	31 (50.0)	31 (50.0)	0.221	32 (51.6)	30 (48.4)	0.057	25 (40.3)	13 (21.0)	24 (38.7)	0.128

[a]For this variable, Fisher's exact test was applied because several expected cell counts were <5. HPF, high-power field; LN, lymph node; p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

Independent prognostic indicators for OS were SAMHD1 expression, and p-ATM (Table V, model 1). STS patients with positive SAMHD1 expression had a 4.178-fold higher risk of mortality than those with negative SAMHD1 expression (95% CI; 1.828-9.548, P=0.002) (Table V, model 1). Furthermore, STS patients with positive p-ATM expression had a 3.420-fold higher risk of mortality than those with negative p-ATM expression (95% CI; 1.518-7.704, P=0.003) (Table V, model 1). Age, M category, and SAMHD1 expression were significant independent factors associated with PFS in the multivariate analysis (Table VI, model 1). The SAMHD1-positive group had a 3.617-fold increased risk of progression or death (95% CI: 2.154-6.074, <0.001) compared to the SAMHD1-negative group (Table VI, model 1).

Only combined SAMHD1 and p-ATM expression was an independent predictor of OS of STS patients (Table V, model 2). STS patients with the SAMHD1+/p-ATM-expression pattern or SAMHD1-/p-ATM+ expression pattern had a 6.588-fold (95% CI; 1.834-23.670, P=0.004) increased risk of death compared to SAMHD1-/p-ATM-cases, while SAMHD1+/p-ATM+ cases showed a 18.915-fold (95% CI; 5.710-62.654, P<0.001) higher risk of death (Table V, model 2). Age, M category and combined expression of SAMHD1 and p-ATM were independent prognostic factors of PFS in STS patients (Table VI, model 2). STS patients with the SAMHD1+/p-ATM- or SAMHD1-/p-ATM+ expression pattern demonstrated a 3.749-fold (95% CI; 1.943-7.233, P<0.001) greater risk of death or progression, whereas SAMHD1+/p-ATM+ cases had a 5.159-fold (95% CI; 2.773-9.597, P<0.001) increased risk of death or progression compared to STS patient with the SAMHD1-/p-ATM-expression pattern (Table VI, model 2).

Discussion

In this study, we evaluated the immunohistochemical expression of SAMHD1 and p-ATM in STS tissues and investigated their associations with clinicopathological features and patient outcomes. Although previous studies have investigated the associations between SAMHD1 and p-ATM expression and prognosis in various cancers (23-25), their prognostic significance in STS has not been explored. To our knowledge, this is the first study to evaluate the prognostic impact of SAMHD1 and p-ATM expression specifically in STS. In the present study, both SAMHD1 and p-ATM exhibited predominant nuclear localization based on immunohistochemical staining. We found that both the individual and combined expression of SAMHD1 and p-ATM were significantly associated with higher histologic grade and adverse survival outcomes in STS patients. Multivariate analysis revealed that both the individual and combined expression of SAMHD1 and p-ATM independently served as prognostic factors for OS. Additionally, SAMHD1 expression and the co-expression pattern of SAMHD1 and p-ATM were independent prognostic factors for PFS. Furthermore, SAMHD1 and p-ATM expression were highly correlated.

SAMHD1, by facilitating DNA end resection at double-strand breaks, plays important roles in DDR and homologous recombination (24). Loss or dysfunction of SAMHD1 can lead to the accumulation of genomic instability and has been associated with tumorigenesis in several

Table IV. Univariate Cox proportional hazards regression analysis of OS and PFS in patients with soft tissue sarcoma.

Characteristics	OS		PFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex, male (vs. female)	0.831 (0.468-1.474)	0.527	0.997 (0.636-1.565)	0.990
Age, >60 years (vs. ≤60 years)	1.141 (0.639-2.037)	0.656	1.742 (1.109-2.736)	0.016
T category 3, 4 (vs. T1, 2)	2.3 (1.288-4.107)	0.005	1.514 (0.943-2.431)	0.086
LN metastasis, present (vs. absent)	1.425 (0.638-3.182)	0.388	0.819 (0.394-1.705)	0.594
M category M1 (vs. M0)	2.481 (1.051-5.853)	0.038	7.623 (3.823-15.200)	<0.001
Histologic grade 2 and 3 (vs. grade 1)	3.237 (1.279-8.910)	0.013	2.344 (1.261-4.357)	0.007
Mitotic count ≥10/10 HPF (vs. 0-9/10 HPF)	1.064 (0.599-1.888)	0.833	1.046 (0.669-1.636)	0.844
Tumor differentiation 2 and 3 (vs. 1)	1.280 (0.506-3.239)	0.602	0.961 (0.494-1.869)	0.907
Tumor necrosis present (vs. absent)	1.267 (0.714-2.247)	0.419	1.059 (0.677-1.657)	0.802
SAMHD1, positive (vs. negative)	7.583 (3.536-16.262)	<0.001	4.621 (2.805-7.614)	<0.001
p-ATM, positive (vs. negative)	7.65 (3.688-15.870)	<0.001	2.939 (1.853-4.661)	<0.001
Combined expression of SAMHD1/p-ATM				
$SAMHD1^+$/p-ATM^- or $SAMHD1^-$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	7.179 (2.001-25.753)	0.002	3.694 (1.926-7.085)	<0.001
$SAMHD1^+$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	22.774 (6.950-74.624)	<0.001	6.213 (3.387-11.398)	<0.001

HPF, high-power field; HR, hazard ratio; LN, lymph node; OS, overall survival; p-ATM, phosphorylated ataxia-telangiectasia mutated; PFS, progression-free survival; SAMHD1, SAM domain and HD domain-containing protein 1.

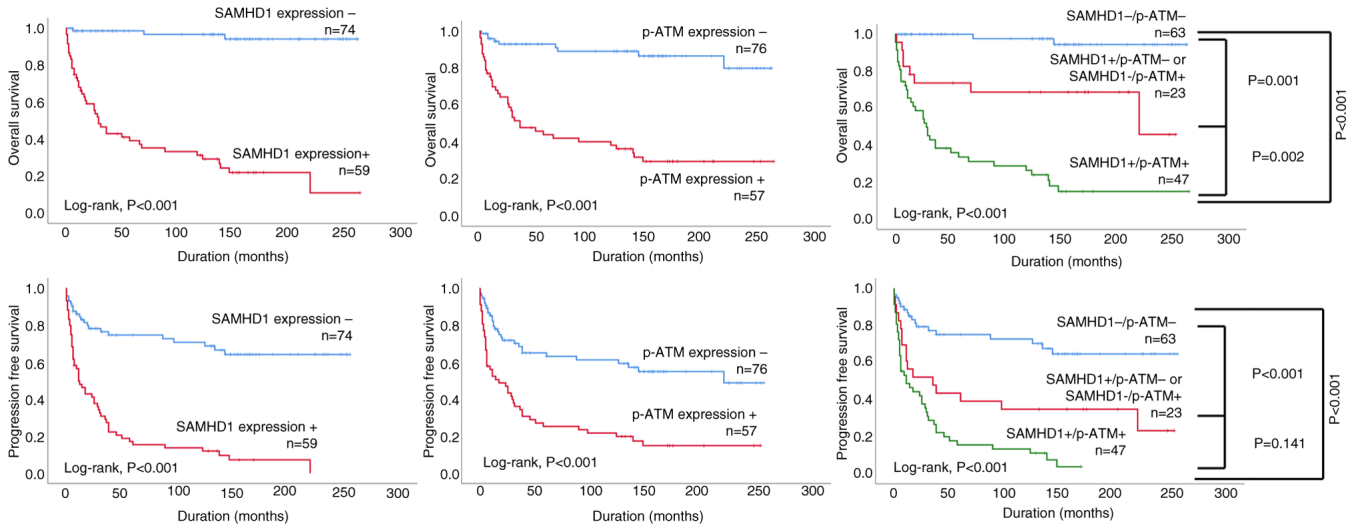


Figure 3. Survival analysis based on the levels of SAMHD1 and p-ATM in patients with soft tissue sarcoma. Kaplan-Meier survival curves for overall survival and progression-free survival of patients with sarcoma according to the individual and co-expression of SAMHD1 and p-ATM. p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

malignancies (30,31). To date, several studies have investigated the impact of SAMHD1 expression on cancer progression across various tumor types, with conflicting results reported depending on the specific cancer type (13-16). In contrast to our findings, decreased SAMHD1 expression has been associated with a poor prognosis in colorectal cancer and diffuse large B-cell lymphoma (13,32). However, numerous studies have reported results consistent with ours. For instance, SAMHD1 expression was associated with shorter time-to-progression and OS in early breast cancer patients treated with neoadjuvant chemotherapy (14). Additionally, SAMHD1 acted as a poor prognostic marker in classical Hodgkin lymphoma (33), aligning with our findings. Taken together, these divergent findings suggest that the prognostic role of SAMHD1 varies depending on tumor type, potentially reflecting cancer-specific differences in biological function and interaction with the tumor microenvironment.

ATM is activated through autophosphorylation in response to DNA double-strand breaks, initiating checkpoint signaling and repair pathways (34). ATM is well recognized for its

Table V. Multivariate Cox proportional hazards regression analysis for OS in patients with soft tissue sarcoma.

	OS	
Characteristics	HR (95% CI)	P-value
Model 1[a]		
SAMHD1, positive (vs. negative)	4.178 (1.828-9.548)	0.002
p-ATM, positive (vs. negative)	3.420 (1.518-7.704)	0.003
Model 2[b]		
Combined expression of SAMHD1/p-ATM		
$SAMHD1^+$/p-ATM^- or $SAMHD1^-$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	6.588 (1.834-23.670)	0.004
$SAMHD1^+$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	18.915 (5.710-62.654)	<0.001

[a]Variables considered in model 1 are T category, M category, histologic grade, SAMHD1 expression and p-ATM expression. [b]Variables considered in model 2 are T category, M category, histologic grade, and combined expression of SAMHD1 and p-ATM. HR, hazard ratio; OS, overall survival; p-ATM, phosphorylated ataxia-telangiectasia mutated; SAMHD1, SAM domain and HD domain-containing protein 1.

Table VI. Multivariate Cox proportional hazards regression analysis for PFS in patients with soft tissue sarcoma.

	PFS	
Characteristics	HR (95% CI)	P-value
Model 1[a]		
Age, >60 years (vs. ≤60 years)	2.038 (1.254-3.313)	0.004
M category M1 (vs. M0)	5.426 (2.575-11.434)	<0.001
SAMHD1, positive (vs. negative)	3.617 (2.154-6.074)	<0.001
Model 2[b]		
Age, >60 years (vs. ≤60 years)	2.180 (1.345-3.534)	0.002
M category M1 (vs. M0)	6.024 (2.863-12.675)	<0.001
Combined expression of SAMHD1/p-ATM		
$SAMHD1^+$/p-ATM^- or $SAMHD1^-$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	3.749 (1.943-7.233)	<0.001
$SAMHD1^+$/p-ATM^+ (vs. $SAMHD1^-$/p-ATM^-)	5.159 (2.773-9.597)	<0.001

[a]Variables considered in model 1 are age, M category, histologic grade, SAMHD1 expression and p-ATM expression. [b]Variables considered in model 2 are age, M category, histologic grade, and combined expression of SAMHD1 and p-ATM. HR, hazard ratio; p-ATM, phosphorylated ataxia-telangiectasia mutated; PFS, progression-free survival; SAMHD1, SAM domain and HD domain-containing protein 1.

role as a tumor suppressor (20). Ataxia-telangiectasia (A-T) is an inherited autosomal recessive disorder resulting from germline mutations in the ATM gene (20,35). Patients with A-T commonly present with neurological and systemic abnormalities, including ataxia of the cerebellum, telangiectasias affecting the skin and eyes, immune dysfunction, and impaired gonadal development (35). In addition to these features, individuals with A-T face a markedly elevated lifetime cancer risk, with approximately 38.2% developing malignancies by the age of 40 (35,36). Although ATM is widely recognized as a tumor suppressor, as previously mentioned, accumulating research suggests that the underlying signaling pathway can, in certain biological contexts, contribute to the advancement of cancer (37). In melanoma, high p-ATM expression was linked to lower 5-year survival and a more aggressive phenotype (21) and was associated with poor locoregional disease-free survival and shorter disease-specific survival in cervical cancer (38), consistent with our findings.

Importantly, our study is among the first to assess the co-expression patterns of SAMHD1 and p-ATM in STS. A moderate-to-strong positive correlation between their expression was observed, supporting previous reports suggesting functional crosstalk between these proteins (19,24,39). SAMHD1 activity has been shown to be modulated by ATM-dependent phosphorylation, and SAMHD1 deficiency can lead to dysregulated ATM signaling and genomic instability (39). The strong prognostic value of the SAMHD1+/p-ATM+ co-expression pattern observed in our study further supports the biological interdependence of these DDR components and suggests that their combined assessment enhances prognostic stratification in STS patients. Considering the findings of the present study, we propose that the DDR plays a critical role in the progression of STS.

STSs can be broadly categorized into two genomic subgroups: i) tumors characterized by extensive copy-number alterations, chromosomal instability, and a high burden of structural variants, and ii) translocation-associated tumors with relatively simple genomes driven by pathognomonic fusion oncoproteins (1). In the former, which is common across adult STSs, chronic replication stress and ongoing DNA damage are intrinsic features of tumor biology (2,3). In tumors with chromosomal instability, persistent DDR signaling may act as a protective mechanism by helping to prevent catastrophic genome collapse, buffering replication stress, and potentially supporting continued proliferation under genotoxic pressure (4). Collectively, these activities make SAMHD1 an attractive tumor promoter and explain why high SAMHD1/p-ATM expression correlates with an increased grade and poorer survival in our STS cohort. p-ATM and SAMHD1 indicate active double-strand break signaling, checkpoint activation, end resection, and homologous recombination at stalled forks and breaks, thereby contributing to the maintenance of genome integrity under stress (5,6). Collectively, these functions suggest that SAMHD1 may act as a tumor promoter and provide a rationale for the observed association between high SAMHD1/p-ATM expression, increased tumor grade, and poorer survival in our STS cohort'.

As mentioned previously, discordant findings have been reported in other malignancies, such as colorectal cancer. In a study investigating the role of SAMHD1 in colorectal cancer, reduced SAMHD1 expression was associated with poor prognosis. The authors demonstrated that the dNTPase function of SAMHD1 suppresses cell proliferation and reduces replication errors, thereby contributing to its tumor-suppressive role. Moreover, mutations affecting SAMHD1's catalytic sites were shown to inhibit the expression of apoptosis-related proteins while upregulating anti-apoptotic factors such as Bcl-2, ultimately suppressing apoptosis and promoting uncontrolled proliferation. We propose that the apparent discrepancy with our study can be explained by the fact that many STS arise under persistent replication stress and pronounced structural instability, conditions in which elevated SAMHD1, together with active ATM signaling, enhances repair capacity and stress tolerance, thereby supporting tumor persistence and progression (1,3). Such cancer-type differences give a reasonable explanation for the different results between our STS study and colorectal cancer.

DDR is fundamentally recognized as a tumor-suppressive mechanism (40). It is activated upon genomic insults such as DNA double-strand breaks, single-strand breaks, or replication stress and serves to arrest the cell cycle, initiate DNA repair, or induce apoptosis or senescence in irreparably damaged cells (40). Through these mechanisms, DDR prevents the accumulation of mutations and maintains genomic stability, acting as a safeguard against malignant transformation (40). However, accumulating evidence suggests that DDR can also exert oncogenic effects under certain biological contexts, giving rise to a paradox in its role in cancer (8). In established tumors, particularly those experiencing high replication stress, DDR activity can support cancer cell survival by managing chronic DNA damage (8). Consequently, an intact DDR pathway can contribute to tumor progression and be associated with poor patient prognosis (8). In light of this, the association between SAMHD1 and p-ATM expression and poor prognosis supports the possibility that an intact or upregulated DDR pathway contributes to tumor progression in STS.

From a clinical standpoint, the identification of SAMHD1 and p-ATM as independent prognostic markers has important implications. These molecules could potentially be incorporated into histopathological assessment to help stratify patients at higher risk, informing decisions regarding closer monitoring or individualized therapeutic strategies. In parallel, there has been increasing interest in targeting components of the DDR as a novel therapeutic avenue in oncology (7). Although PARP inhibitors have demonstrated clinical benefit in tumors harboring homologous recombination deficiencies, the therapeutic relevance of modulating SAMHD1 or ATM activity in this context remains to be fully elucidated (26). Further research is warranted to explore whether inhibition of SAMHD1 or ATM could enhance the therapeutic efficacy of chemotherapy or radiotherapy in STS.

Our study has several limitations. The retrospective design and the use of tissue microarrays limit the generalizability of our findings. Moreover, the synergistic correlation between SAMHD1 and p-ATM in the current study depends on immunohistochemical and clinical evidence, and there is no functional evidence directly supporting it. Further in vitro and in vivo experiments, such as co-knockdown or overexpression studies, are warranted to explore the underlying biological mechanism of the interaction between them and the effects on tumor cell proliferation, apoptosis, and DNA repair ability. In addition, the relatively small cohort size and the critical underrepresentation of certain histological subtypes may limit the statistical power of our analyses and compromise the generalizability of subtype-specific conclusions. Larger, multi-institutional studies are required to validate and extend our findings.

In conclusion, we investigated the expression of SAMHD1 and p-ATM in patients with STS and found that their expression is significantly associated with aggressive tumor characteristics and poor clinical outcomes. Their individual and combined expression patterns were independent prognostic factors for OS and PFS. These findings provide new insights into the molecular pathology of STS and suggest that DDR components such as SAMHD1 and p-ATM can serve as valuable prognostic biomarkers and potential therapeutic targets in this challenging-to-treat malignancy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

YJK and KMK conceived and designed the study, and performed the experiments. YJM contributed to the acquisition of clinical samples, participated in pathological review and assisted in the interpretation of clinical data. KYJ, ARA, MJC and WSM analyzed the data. YJM, ARA, MJC and KYJ were involved in statistical analysis, data visualization and interpretation of the results. YJK and KMK drafted the manuscript. ARA, HSP, MJC and WSM verified the authenticity of all the raw data, assisted in data curation and validation, contributed to the interpretation of the findings, and critically revised the manuscript for important intellectual content. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study was conducted in accordance with The Declaration of Helsinki and approved by the Institutional Review Board of Jeonbuk National University Hospital (approval no. 2024-04-026-001; Jeonju, South Korea). The requirement for consent for participation was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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