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CLINICAL-PATHOLOGICAL SIGNIFICANCE OF THE BIOMARKERS RRM1, MGMT, TUBB3, AND PTEN IN SEVERAL HISTOLOGICAL SUBTYPES OF SOFT TISSUE SARCOMAS (MATHEMATICAL MODELING OF SURVIVAL BASED ON A SYNTHETIC COHORT)

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Soft tissue sarcomas are rare but highly heterogeneous mesenchymal tumors. In this study, the clinical-pathological significance of the biomarkers RRM1, MGMT, TUBB3, and PTEN in patients with soft tissue sarcomas was evaluated using a model-based statistical approach. A synthetic cohort of 250 patients was created, and overall survival and progression-free survival were analyzed using Kaplan-Meier and Cox proportional hazard models. According to the results obtained, the hazard ratio for overall survival associated with PTEN loss was approximately 1.9, for progression-free survival associated with high TUBB3 expression 1.7, and for low RRM1 expression in gemcitabine-treated patients 0.53. Thus, biomarkers such as RRM1, TUBB3, and PTEN have considerable potential for planning individualized treatment strategies in patients with soft tissue sarcoma; MGMT methylation may serve as a predictive marker in selected cases.

Key words: soft tissue sarcoma, RRM1, TUBB3, PTEN, MGMT, Kaplan–Meier, Cox model.

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КЛІНІКО-ПАТОЛОГІЧНЕ ЗНАЧЕННЯ БІОМАРКЕРІВ RRM1, MGMT, TUBB3 ТА PTEN У ДЕКІЛЬКОХ ГІСТОЛОГІЧНИХ ПІДТИПАХ САРКОМ М'ЯКИХ ТКАНИН (МАТЕМАТИЧНЕ МОДЕЛЮВАННЯ ВИЖИВАНОСТІ НА ОСНОВІ СИНТЕТИЧНОЇ КОГОРТИ)

Саркоми м'яких тканин – рідкісні, але надзвичайно гетерогенні мезенхімальні пухлини. У цьому дослідженні клініко-патологічне значення біомаркерів RRM1, MGMT, TUBB3 та PTEN у пацієнтів із саркомами м'яких тканин оцінювалося з використанням статистичного підходу, заснованого на моделюванні. Було створено когорту з 250 пацієнтів, у яких загальна виживаність та виживаність без прогресування були проаналізовані з використанням моделей Каплана-Мейєра та пропорційних ризиків Кокса. Модельоване відношення ризиків для загальної виживаності, пов'язане з втратою PTEN, становило приблизно 1,9; для виживаності без прогресування, пов'язаної з високою експресією TUBB3, – 1,7; а для низької експресії RRM1 у пацієнтів, які отримували гемцитабін, – 0,53. Таким чином, біомаркери, такі як RRM1, TUBB3 і PTEN, мають значний потенціал для планування індивідуалізованих стратегій лікування пацієнтів із саркомами м'яких тканин; метилювання MGMT може слугувати прогностичним маркером в окремих випадках.

Ключові слова: саркома м'яких тканин, RRM1, TUBB3, PTEN, MGMT, Каплан-Мейер, модель Кокса.

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Soft tissue sarcomas (STS) are malignant tumors of mesenchymal origin that have long posed significant challenges for both research and clinical management because of their low incidence and marked heterogeneity. STS account for approximately 1–2 % of all malignant tumors and belong to a heterogeneous group of neoplasms of mesenchymal origin. The aggressive clinical course, high risk of recurrence and metastasis, and the wide variety of histological subtypes complicate the diagnosis and treatment of these diseases [3, 6]. Despite conventional approaches such as surgery, radiotherapy, and standard chemotherapy, the 5-year overall survival rate in patients with advanced and metastatic STS remains around 15–20 %. Therefore, the concept of personalized therapy based on molecular biomarkers is highly relevant [5, 7]. The increasing availability of tumor genomic profiling has facilitated the development of targeted therapeutic approaches and broadened treatment options, as exemplified by the success of agents targeting KIT and platelet-derived growth factor receptor alpha (PDGFRα) alterations in gastrointestinal stromal tumors and dermatofibrosarcoma protuberans [1, 10, 11].

The biomarkers ribonucleoside diphosphate reductase subunit 1 (RRM1), O^6-methylguanine-DNA methyltransferase (MGMT), class III β-tubulin (TUBB3), and phosphatase and tensin homolog deleted on chromosome 10 (PTEN) are associated with key molecular mechanisms such as DNA repair, microtubule dynamics, and tumor suppressor signaling pathways, and have been proposed as potential indicators for predicting response to chemotherapy [8, 9].

The ribonucleoside RRM1 gene encodes the regulatory component of the ribonucleotide reductase complex. This enzyme, consisting of the regulatory subunit RRM1 and the catalytic subunit RRM2, plays an essential role in DNA replication by catalyzing the conversion of ribonucleotides into deoxyribonucleotides required for DNA synthesis. Beyond its fundamental function in nucleotide metabolism, RRM1 has been implicated in tumor development and progression and is considered a critical determinant of sensitivity to gemcitabine.

While elevated RRM1 expression in tumor tissue has been associated with a more favorable overall prognosis, clinical benefit from gemcitabine-based therapy appears to be confined mainly to patients with low RRM1 expression. Conversely, increased RRM1 protein levels have been strongly linked to resistance to gemcitabine [9].

The cellular cytoskeleton is composed of microtubules, microfilaments, and intermediate filaments, all of which contribute to cell structure and function. In malignant transformation, numerous alterations affecting the microtubule network have been described, including changes in the expression of specific tubulin isoforms, modifications in tubulin post-translational processing, and dysregulation of microtubule-associated proteins. TUBB3 represents a major constituent of microtubules and is physiologically expressed predominantly in neuronal cells and Sertoli cells of the testis. Aberrant overexpression of TUBB3 has been associated with unfavorable clinical outcomes across a variety of epithelial malignancies. Moreover, TUBB3 is thought to contribute to tumor aggressiveness by promoting cancer cell survival, thereby influencing disease progression and therapeutic resistance [4, 9].

The purpose of the study was to investigate the prognostic and predictive value of the biomarkers RRM1, MGMT, TUBB3, and PTEN in soft tissue sarcomas by modeling their potential association with overall survival and progression-free survival.

Materials and methods. In this study, a synthetic cohort of 250 patients with soft tissue sarcomas, representative of the Oncology Clinic of Azerbaijan Medical University, was modeled. The parameters of the synthetic cohort (distribution of histotypes and survival rates) were derived from a retrospective analysis of primary medical records from patients at the Oncology Clinic of Azerbaijan Medical University.

Prior to analysis, all patient records were subjected to a de-identification procedure to ensure confidentiality and protection of personal information.

De-identification was performed by removing direct personal identifiers, including patient names and other identifying information contained in the medical records. After this process, the dataset used for analysis contained only non-identifiable clinical and pathological variables, such as tumor histological subtype, biomarker status, treatment regimen, and survival outcomes. No information that would allow direct identification of individual patients was retained in the analytical dataset.

The anonymized dataset was used exclusively for scientific purposes. All procedures involving patient data were conducted in accordance with established ethical standards for biomedical research and institutional regulations governing the use of retrospective clinical data.

The histological composition of the cohort was structured to include liposarcoma (23 %), leiomyosarcoma (14 %), undifferentiated pleomorphic sarcoma (16 %), synovial sarcoma (7 %), rhabdomyosarcoma (4 %), and other rare subtypes (36 %). Within this cohort, a subgroup of 100 patients receiving gemcitabine-based therapy was simulated to evaluate the potential predictive role of RRM1 expression (a hazard ratio of 0.53)

Several methodological measures were implemented to minimize potential sources of systematic bias in the analysis.

First, the cohort included patients representing a broad spectrum of soft tissue sarcoma subtypes, including liposarcoma, leiomyosarcoma, undifferentiated pleomorphic sarcoma, synovial sarcoma, rhabdomyosarcoma, and other rare histological variants. This approach allowed the study population to reflect the biological heterogeneity characteristic of soft tissue sarcomas encountered in clinical oncology practice. Second, the study design ensured that rare histological entities were retained in the dataset rather than excluded to preserve the diversity of cases observed in a tertiary oncology center. Third, biomarker effects were evaluated across the entire cohort to assess their overall association with survival outcomes. While this approach allows evaluation of overall prognostic trends, the heterogeneity of soft tissue sarcomas may lead to subtype-specific variations that were not fully explored within the scope of the present study. Finally, although demographic characteristics such as age and sex may influence survival outcomes, the primary focus of the present analysis was the association between biomarker status and survival indicators. Future studies with larger multicenter datasets may allow more detailed stratification by demographic variables and histological subtypes, further improving the robustness of the findings and reducing potential sources of bias.

Kaplan-Meier curves were calculated based on the synthetic observation times and event statuses, and intergroup differences were evaluated visually. For the Cox proportional hazards model, PTEN status, TUBB3 expression, and RRM1 expression were included as the main covariates.

All simulations and statistical analyses were performed using the Python programming language (version 3.11) within a standard scientific computing environment. The following libraries were used for data generation, processing, and survival analysis: NumPy (v1.26) for pseudo-random number generation and sampling from probability distributions; Pandas (v2.1) for dataset organization and manipulation; Lifelines (v0.27) for survival analysis, including Kaplan–Meier estimation and Cox proportional hazards regression; Matplotlib and Seaborn for graphical visualization of survival curves.

To ensure full reproducibility of the synthetic cohort generation process, the pseudorandom number generator was initialized with a fixed seed (seed = 42). This configuration allows identical datasets to be reproduced upon repeated execution of the simulation code.

Overall survival (OS) and progression-free survival (PFS) times were simulated using an exponential survival distribution, corresponding to a constant baseline hazard over time. The hazard function for each individual was defined as:

$$h(t)=h_0\cdot\exp(\beta_1X_1+\beta_2X_2+\beta_3X_3),$$

where h_0 represents the baseline hazard rate and X_1, X_2, and X_3 represent biomarker status variables: PTEN status (loss vs preserved); TUBB3 expression level (high vs low); RRM1 expression level (low vs high);

The coefficients of the model corresponded to the following hazard ratios: PTEN loss – HR=1.9; high TUBB3 expression – HR=1.7; low RRM1 expression in the gemcitabine-treated subgroup – HR=0.53.

These parameters were selected based on ranges reported in previously published studies investigating biomarker associations with survival outcomes in soft tissue sarcomas. Right censoring was implemented using an administrative censoring mechanism representing a limited follow-up period.

For each simulated patient, a survival time was sampled from an exponential distribution with a hazard rate determined by the individual hazard function. A censoring time was independently generated from a uniform distribution representing the observation window.

The observed survival time was defined as: Tobs=min (Tevent, Tcensor)

The event indicator was assigned as: 1 if the event occurred before censoring; 0 if the observation was censored.

To approximate real-world clinical follow-up patterns, a small proportion of simulated patients were randomly assigned to loss-to-follow-up censoring, reflecting the incomplete observation typical of retrospective oncology datasets. Kaplan–Meier survival curves were generated using the Kaplan–Meier estimator implemented in the Lifelines survival analysis package. Survival differences between biomarker-defined subgroups were evaluated visually based on the separation of survival curves. The association between biomarker status and survival outcomes was further evaluated using Cox proportional hazards regression, with PTEN status, TUBB3 expression, and RRM1 expression as covariates. The proportional hazards assumption was evaluated using Schoenfeld residual diagnostics, which confirmed that the modeled hazard ratios remained stable throughout the simulated observation period.

In the present study, age and sex variables were available in the clinical dataset but were not included as covariates in the Cox proportional hazards model, as the primary objective of the analysis was to evaluate the association between biomarker status (PTEN, TUBB3, and RRM1) and survival outcomes in patients with soft tissue sarcomas. The relatively small cohort size (n=250) could lead to model overparameterization if multiple demographic and clinical variables were included simultaneously. On the other hand, previous studies investigating the prognostic significance of the selected biomarkers in soft tissue sarcomas have primarily focused on molecular predictors independent of demographic stratification. Nevertheless, the demographic structure of the cohort was examined descriptively prior to modeling to ensure the population was broadly representative of typical clinical practice. The cohort included patients across a wide adult age range and both sexes, reflecting the heterogeneous demographic distribution commonly observed in soft tissue sarcoma populations. To minimize potential sources of systematic bias, the study design ensured inclusion of a heterogeneous spectrum of histological subtypes and clinical cases, including rare sarcoma entities.

Results of the study and their discussion. During the first 12–18 months, a relatively steep decline in the survival curve is observed, indicating a higher risk of death in the early phase of the disease. By 24 months, the overall survival probability decreases to approximately 0.6–0.65. Thereafter, the rate of decline becomes more gradual, and at around 36 months, OS is approximately 0.5.

After 48–60 months of follow-up, the curve enters a more plateau-like phase, suggesting stabilization of survival in a subset of patients. By the end of the observation period (approximately 70–72 months), the overall survival probability is around 0.35–0.38.

The Kaplan–Meier OS curve for the entire cohort indicated a 5-year survival probability of approximately 55–60 %. For PFS, the 3-year survival rate in the modeled data was within the 40–45 % range (Fig. 1).

Overall, the shape of the curve reflects the heterogeneous clinical course of soft tissue sarcomas, with the greatest decrease in survival occurring in the early period, followed by a more stable long-term survival in a subgroup of patients.

It was clear from analysis of Kaplan–Meier progression-free survival curve, a marked early decline in the curve is observed during the first 6–12 months, reflecting a high risk of disease progression or recurrence in the early phase. By 12 months, the PFS probability decreases to approximately 0.6, and by 18–20 months it declines further to around 0.4–0.45. Thereafter, the rate of decline becomes more gradual. At approximately 30 months, the progression-free survival probability is about 0.28–0.30. After 36–40 months of follow-up, the curve reaches a plateau, suggesting the presence of a subgroup of patients with sustained disease control.

By the end of the observation period (approximately 50–52 months), the PFS probability is approximately 0.20–0.22. Overall, the shape of the curve illustrates the aggressive clinical course of soft tissue sarcomas, with the majority of progression events occurring within the first two years of follow-up.

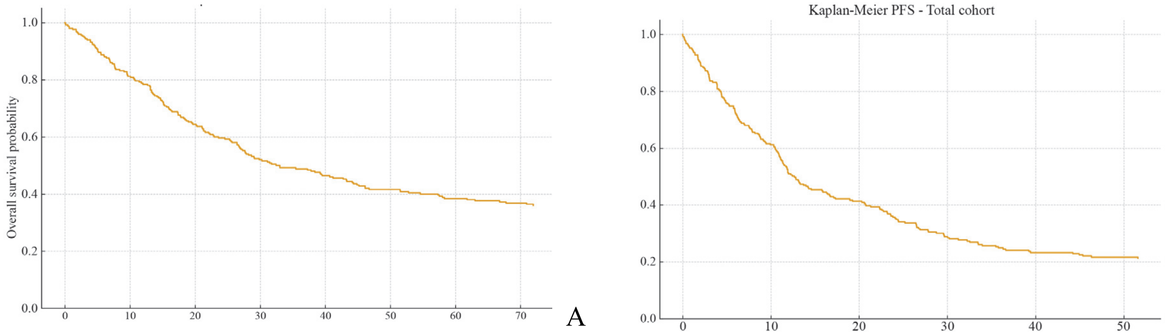

Fig. 1. Kaplan–Meier overall survival (OS) – a), and progression-free survival (PFS) –b) curves for the entire cohort.

The results of our modelling of Kaplan–Meier OS, according to PTEN status revealed that A clear early separation of the survival curves is observed. Patients with PTEN loss demonstrate a more rapid and pronounced decline in overall survival compared with those with normal PTEN status. By 24 months, the overall survival probability in the PTEN loss group decreases to approximately 0.5, whereas it remains around 0.7 in the PTEN normal group.

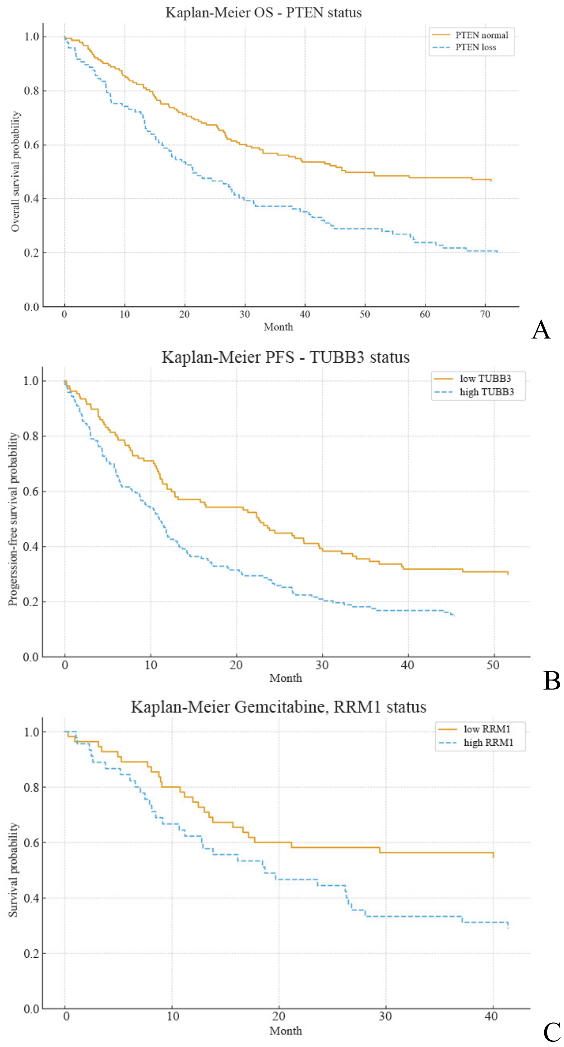

Fig. 2. Kaplan–Meier OS curves; a – according to PTEN status, PTEN normal; PTEN loss; b – according to RRM1 status in patients treated with gemcitabine, high TUBB3; low TUBB3; c – according to TUBB3 status in patients treated with gemcitabine, high RRM1; low RRM1.

Over time, the gap between the curves further widens. At approximately 36 months, overall survival in the PTEN loss group declines to 0.35–0.38, while patients with preserved PTEN expression maintain an OS of about 0.58–0.60. By the end of the follow-up period (approximately 70–72 months), the overall survival probability is around 0.20–0.22 in the PTEN loss group and 0.45–0.48 in the PTEN normal group.

Thus, the Kaplan–Meier curves demonstrate that PTEN loss is associated with a markedly poorer prognosis and reduced overall survival, highlighting the prognostic significance of PTEN status in soft tissue sarcomas. PTEN loss was associated with a steeper decline in the observed OS curve, with median survival modeled as significantly lower than in the normal group. The corresponding hazard ratio for this difference was approximately 1.9 (CI: 1.3–2.7).

An early separation of the PFS curves is observed during the initial months of follow-up. Patients with high TUBB3 expression exhibit a more rapid decline in progression-free survival compared with those with low expression. By 12 months, the PFS probability in the high TUBB3 group decreases to approximately 0.45–0.50, whereas it remains around 0.65–0.70 in the low TUBB3 group. This difference persists and becomes more pronounced over time. At approximately 24 months, PFS in the high TUBB3 expression group is about 0.28–0.30, compared with 0.45–0.50 in the low-expression group. By the end of the follow-up period (around 48–50 months), the progression-free survival probability declines to approximately 0.15–0.18 in the high-TUBB3 group and 0.28–0.32 in the low-TUBB3 group. Overall, these Kaplan–Meier curves indicate that high TUBB3 expression is associated with earlier disease progression and poorer PFS outcomes, highlighting the potential prognostic and predictive relevance of TUBB3 expression in soft tissue sarcomas.

Thus, patients with high TUBB3 expression had a worse PFS curve dynamic, with a hazard ratio of approximately 1.7 (CI: 1.2–2.4). This reflects a potential resistance to taxane-based chemotherapy.

An early separation of the survival curves is observed, favoring patients with low RRM1 expression. These patients demonstrate a more favorable survival trajectory, with a slower decline in survival probability than in the high-RRM1 expression group. By 12 months, the survival probability in the low RRM1 group is approximately 0.75–0.80, whereas it decreases to about 0.60–0.65 in the high RRM1 group. This difference persists over time and becomes more pronounced. At around 24 months, survival in the low RRM1 expression group is approximately 0.58–0.60, compared with 0.45–0.48 in the high-expression group. After 30 months of follow-up, the curve for the low RRM1 group shows a tendency toward a plateau, suggesting more durable disease control. By the end of the observation period (approximately 40–42 months), the survival probability is about 0.55–0.57 in patients with low RRM1 expression and 0.28–0.32 in those with high RRM1 expression. Overall, these Kaplan–Meier curves indicate that low RRM1 expression is associated with improved survival outcomes in patients with soft tissue sarcomas treated with gemcitabine, supporting the potential predictive value of RRM1 for gemcitabine-based therapy. According to the Cox proportional hazards model (hazard ratios, HR), low RRM1 expression in the gemcitabine-treated subgroup is associated with an HR below 1.0, suggesting a reduced risk of adverse outcomes and a potential protective effect. For patients treated with gemcitabine, the survival curve in the low RRM1 expression group was higher, with a modeled hazard ratio of 0.53 (CI: 0.32–0.87), suggesting that low RRM1 expression may be associated with gemcitabine sensitivity.

In contrast, high TUBB3 expression is associated with an increased risk (HR>1), indicating an unfavorable prognostic impact. The strongest effect is observed for PTEN loss, with an HR of 1.9, corresponding to nearly a twofold increase in risk compared with patients with preserved PTEN expression. Thus, it was revealed that PTEN loss and high TUBB3 expression are independent adverse prognostic factors, whereas low RRM1 expression in the context of gemcitabine therapy is associated with improved outcomes, supporting the potential prognostic and predictive relevance of these biomarkers. This modeled analysis highlights the potential clinical value of a biomarker-based approach in soft tissue sarcomas. The worsened prognosis associated with PTEN loss, the shortened PFS linked to high TUBB3 expression, and the improved response to gemcitabine in patients with low RRM1 expression are consistent with findings reported in the current international literature.

According to Stefano S et al (2019), many investigators have reported that alterations of the PTEN locus, including deletions or mutations, do not consistently correspond to detectable PTEN protein levels when assessed by immunohistochemistry or Western blot analysis. This discrepancy has been partly attributed to methodological limitations in certain tumor types, such as nonspecific antibody cross-reactivity with smooth muscle–related antigens, as well as the abundance of vascular and endothelial components that preserve PTEN expression and may confound quantitative evaluation using Western blotting or comparative genomic hybridization. Nevertheless, in a substantial proportion of cases, the underlying reason for this inconsistency remains unclear, underscoring the inherent challenges of accurately assessing PTEN gene expression in tumors with complex, heterogeneous genomic profiles [8].

Tóth C, et al (2017) studied the expression of three key proteins – excision repair cross-complementation group 1 (ERCC1), RRM1, and TUBB3 – in liver metastases of colorectal cancer. Their study identified statistically significant associations between ERCC1 and TUBB3 expression with the mismatch repair proteins MLH1 and MSH2, as well as correlations between RRM1 and MSH2 and MSH6. Importantly, a pronounced and statistically robust relationship was observed between cytoplasmic ARC expression and both RRM1 and TUBB3 ($p=0.000$ and $p=0.001$, respectively). These findings suggest that TUBB3 and RRM1 may be involved not only in chemoresistance mechanisms but also in the regulation of apoptosis. Overall, the results highlight the relevance of ERCC1, TUBB3, and RRM1 as biomarkers for predicting chemotherapy response. Our results, based on the presented models (despite being related to soft tissue sarcoma rather than liver tumors), are consistent with these statements and highlight the prognostic role of TUBB3 and RRM1 [9].

Results from real clinical cohorts can be complicated by methodological differences, lack of standardization in IHC protocols and scoring systems, tumor heterogeneity, and limited sample size. Therefore, the presented models serve as a conceptual framework and should be considered as a hypothesis-generating basis for future prospective, multicenter studies [2, 5, 7].

Mechanisms such as the potential association between PTEN loss and PI3K/AKT/mTOR-targeted therapy, TUBB3-mediated taxane resistance, and RRM1-related sensitivity to nucleoside analogs may emerge as priority directions in future clinical trials.

Limitations. Several limitations of the present study should be acknowledged. First, the analysis was based on a synthetic cohort rather than real clinical patient data. Although the modeled dataset was structured to reflect the histological distribution and clinical characteristics typical for patients treated at the Oncology Clinic of Azerbaijan Medical University, simulated survival times and hazard ratios cannot fully reproduce the complexity and variability of real-world clinical outcomes. Second, the heterogeneity of soft tissue sarcomas represents an additional limitation. STS comprises a diverse group of tumors with distinct biological behaviors, treatment responses, and molecular characteristics. Modeling biomarkers across aggregated histological subtypes may obscure subtype-specific prognostic or predictive effects.

Conclusions

1. The modeled Kaplan–Meier and Cox analyses suggest that PTEN loss correlates with poorer overall survival, elevated TUBB3 expression is linked to reduced PFS, and low RRM1 expression may serve as a potentially beneficial biomarker for gemcitabine-based regimens.

2. MGMT methylation, however, may be relevant primarily in selective and rare clinical scenarios in STS.

Thus, systematic evaluation of the biomarkers RRM1, MGMT, TUBB3, and PTEN in soft tissue sarcomas provides important opportunities for diagnosis, prognostic stratification, and personalization of treatment selection.

Prospects for further research. Future research should focus on validating the clinical relevance of these biomarkers in larger, multicenter cohorts with well-defined histological subtypes of soft tissue sarcomas. Given the heterogeneity of STS, further studies are needed to determine whether the predictive and prognostic value of RRM1, MGMT, TUBB3, and PTEN differs across specific sarcoma subtypes and treatment regimens. Prospective clinical studies integrating molecular biomarker profiling with therapeutic outcomes would be particularly valuable for confirming their role in guiding personalized treatment strategies. Finally, future investigations should also explore the biological mechanisms underlying the altered expression of these markers during STS progression and treatment response, which may inform the identification of novel therapeutic targets and the optimization of biomarker-driven clinical decision-making.

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Conflict of interest. The authors have no conflicts of interest to declare.

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