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Clinical–Genomic AI Risk Assessment for Sarcoma: A Retrospective Study on TCGA Cohorts

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Abstract

Background: Soft tissue sarcomas account for roughly 80% of sarcoma cases and are often diagnosed late due to nonspecific symptoms, with median diagnostic delays of 4-6 months contributing to poor outcomes. We retrospectively evaluated an AI-driven clinical–genomic risk assessment tool on publicly available cohorts to assess its ability to flag sarcoma without reliance on symptom reporting.

Methods: We assembled 159 confirmed soft tissue sarcoma cases from TCGA and 300 non-sarcoma controls equally drawn from kidney, breast, and skin cancer cohorts. Clinical data were parsed from GDC clinical XML files and pathology reports; molecular data consisted of normalized RNA-seq counts from TCGA sarcoma samples and baseline normal tissue expression from GTEx. A proprietary ensemble algorithm fused structured clinical variables (demographics, laboratory values, tumor size and depth, pathology descriptors) with gene-expression thresholds tied to known sarcoma markers. Performance metrics—sensitivity, specificity, and overall accuracy—were computed on the combined cohort.

Results: The model correctly flagged 73 of 159 sarcoma cases (45.9% sensitivity) and produced zero false positives among 300 controls (100% specificity), yielding an overall accuracy of 78.9%. Detection spanned AJCC stages 0–4, with notable success in stages 1-2, demonstrating stage-spanning capability.

Key predictors included anatomical depth, tumor size, platelet count, and expression of proliferation-associated transcripts.

Conclusions: In this retrospective TCGA validation, the risk assessment tool achieved perfect specificity and moderate sensitivity for soft tissue sarcoma detection without symptom inputs. This performance profile indicates potential feasibility for clinical decision support applications where high confidence in positive flags is essential. Future work will extend validation to bone sarcomas via pediatric oncology partnerships and prospective clinical studies.

Keywords: Sarcoma; AI; Risk stratification; TCGA; Soft tissue; Clinical–genomic integration; Early detection; Clinical Decision support

Introduction

Soft tissue sarcomas (STS) comprise approximately 80% of all sarcoma presentations and pose significant diagnostic challenges due to their relative rarity and nonspecific early symptoms. With an annual incidence of approximately 13,500 cases in the United States and 23,000 in Europe, STS represent less than 1% of all adult malignancies but account for disproportionate morbidity and mortality due to late-stage diagnosis [1,2]. Median diagnostic delay from symptom onset to definitive diagnosis ranges from 4-6 months, with up to 25% of patients experiencing delays exceeding one year [3,4]. Five-year survival rates for localized disease (83%) drop precipitously for regional (54%) and distant metastatic disease (16%), underscoring the critical importance of early detection [5]. Traditional detection pathways rely heavily on symptomatic patients seeking care, followed by imaging studies and ultimately tissue diagnosis. However, early-stage STS often present with vague symptoms such as fatigue, mass effect, or nonspecific pain that may be attributed to more common conditions [6]. This diagnostic challenge is compounded by the rarity of STS, leading to lower clinical suspicion among primary care providers. Recent advances in artificial intelligence and multi-modal data integration present new opportunities for earlier detection. Prior studies have explored either structured electronic health record (EHR) data [7,8] or transcriptomic signatures alone [9,10], with moderate success. However, few have validated a combined clinical–genomic model on public cohorts or assessed feasibility for integration into clinical workflows. A study by Chen et al. demonstrated that integrated models outperformed single-modality approaches in rare cancer detection, achieving 15-20% higher sensitivity at equivalent specificity levels [11]. We therefore performed a retrospective evaluation of our ensemble risk assessment tool on TCGA cohorts to gauge feasibility for early sarcoma detection. This study aims to address the hypothesis that integration of clinical

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variables with genomic markers can identify STS cases across all stages without reliance on symptomatic presentation, potentially enabling earlier intervention through targeted workups of high-risk individuals.

Materials and Methods

Cohort Assembly

Soft Tissue Sarcoma Cases (n = 159): Confirmed adult TCGA-SARC samples spanning multiple histological subtypes, including leiomyosarcoma (n = 53), dedifferentiated liposarcoma (n = 37), undifferentiated pleomorphic sarcoma (n = 31), myxofibrosarcoma (n = 17), synovial sarcoma (n = 10), and other subtypes (n = 11). Samples represented all AJCC stages (0-4).

Controls (n = 300): Equal subsets (n = 100 each) from TCGA-KIRC+KIRP (kidney), TCGA-BRCA (breast), and TCGA-SKCM (skin melanoma). Control selection criteria included matched age distribution and data completeness for clinical variables.

Data Extraction and Processing

Clinical Variables: Extracted demographics, tumor size, anatomical depth, laboratory measures (CBC, metabolic panels), and pathology report descriptors via combined manual and automated parsing of GDC clinical XML and PDF files. Missing values (7.3% overall) were imputed using multiple imputation by chained equations.

- Molecular VariableSarcoma cases: Upper-quartile normalized, $\log_2$-transformed RNA-seq counts from TCGA-SARC.

- Normal baseline: GTEx normal tissue expression for the same gene set to establish marker thresholds.

- Feature selection: Differential expression analysis identified 127 genes with significant expression changes in sarcoma versus matched normal tissues (FDR < 0.05, $|\log_2 FC| > 1.5$).

Model Framework

The risk assessment system employs a proprietary two-stage ensemble approach that combines clinical and genomic data streams:

Clinical Module: A gradient-boosted decision tree model processes approximately 50 structured clinical features, generating a continuous risk score. Features include demographic information, laboratory values, imaging characteristics (when available), and histopathological descriptors. The module was trained with regularization parameters to prevent overfitting.

Genomic Module: This component evaluates expression patterns of established sarcoma-associated genes, including proliferation markers, differentiation factors, and pathway modulators. A combination of continuous risk contributions and binary threshold-based flags contributes to this module's output.

Meta-classifier Integration: A logistic regression meta-classifier fuses outputs from both modules to generate a final risk score. Calibration ensures high specificity by prioritizing precision over recall.

While specific implementation details and computational parameters remain proprietary, the general architecture follows established principles for clinical risk prediction models. The system operates without requiring symptom input data, focusing instead on objective clinical and molecular measurements.

Performance Evaluatio

- **Sensitivity (True Positive Rate)**: Proportion of sarcoma cases flagged.

- **Specificity (True Negative Rate):** Proportion of controls unflagged.

- **Overall Accuracy:** (TP + TN) / Total samples.

- **Subgroup Analysis:** Performance was evaluated across histological subtypes and AJCC stages.

All metrics were computed on the held-out cohort in a one-pass retrospective analysis. No post-hoc threshold adjustments were made to optimize performance metrics.

Results

Overall Performanc

- **Sensitivity:** 45.9% (73/159)

- **Specificity:** 100% (0/300)

- **Accuracy:** 78.9% (373/459)

Performance by Disease Stage

The model demonstrated stage-spanning detection capability, with positive flags distributed across all AJCC stages:

- Stage 0-1: 38.7% sensitivity (12/31)

- Stage 2: 47.2% sensitivity (25/53)

- Stage 3: 51.4% sensitivity (19/37)

- Stage 4: 44.7% sensitivity (17/38)

Notably, the model maintained performance across early stages, with comparable sensitivity for Stage 0-1 cases relative to more advanced disease.

Performance by Histological Subtype

Sensitivity varied across histological subtypes:

- Leiomyosarcoma: 52.8% (28/53),

- Dedifferentiated liposarcoma: 43.2% (16/37),

- Undifferentiated pleomorphic sarcoma: 48.4% (15/31),

- Myxofibrosarcoma: 41.2% (7/17),

- Synovial sarcoma: 30.0% (3/10),

- Other subtypes: 36.4% (4/11).

Feature Importance

Highest-impact features by mean contribution were:

1. Anatomical depth (deep vs. superficial),

2. Tumor size (maximum diameter),

3. Platelet count,

4. Expression levels of proliferation-associated genes,

5. Neutrophil-to-lymphocyte ratio.

The combined model leveraged interactions between clinical and genomic features, with certain patterns showing synergistic effects that enhanced detection capability.

Discussion

Principal Findings

This retrospective study demonstrates that a combined clinical–genomic AI tool can flag soft tissue sarcoma cases with perfect specificity (100%) and moderate sensitivity (45.9%), without relying on symptom reporting. The high specificity is particularly noteworthy, as it suggests the potential for this approach to enhance screening protocols without generating excessive false positives that could lead to unnecessary interventions.

The stage-spanning nature of detection, with comparable sensitivity across early and advanced disease, supports the tool's potential utility for early identification. By achieving 38.7% sensitivity for Stage 0-1 sarcomas, the model demonstrates promise for detecting disease before progression to later stages where outcomes are significantly poorer.

Comparison with Prior Work

Our findings compare favorably with previous studies in rare cancer detection. Ye et al. [12] reported 32% sensitivity at 98% specificity using clinical variables alone for sarcoma detection, while Zhang et al. [13] achieved 40% sensitivity at 94% specificity using genomic markers. Our improved performance metrics likely reflect the synergistic benefit of combining both data modalities in a single framework.

The perfect specificity achieved across multiple control cancer types is particularly notable, as it addresses a common limitation of previous cancer detection algorithms that often demonstrate lower specificity when tested against other malignancies versus healthy controls [14-20].

Clinical Implications and Feasibility Assessment

Potential Clinical Applications:

The risk assessment tool demonstrates characteristics that support potential clinical applications:

- **Enrichment of diagnostic pathways:** The high specificity suggests utility in prioritizing patients for specialist referral and advanced imaging.
- **Complementary screening:** For high-risk populations (e.g., individuals with hereditary syndromes predisposing to sarcoma), the tool could complement existing surveillance protocols.
- **Decision support for indeterminate cases:** The tool might provide additional context for ambiguous clinical or pathological presentations.

Implementation Feasibility:

Several factors influence the feasibility of clinical implementation:

1. Data availability: The model requires both clinical and molecular data, which may not be routinely collected in all settings. However, increasing adoption of molecular profiling in oncology may mitigate this limitation over time.

2. Workflow integration: The tool is designed to integrate with existing EHR systems through standard HL7 interfaces, requiring minimal workflow disruption.

3. Computational requirements: Analysis can be performed within clinically relevant timeframes (<10 minutes) on standard computing infrastructure.

4. Regulatory considerations: As a clinical decision support tool that does not make autonomous diagnostic determinations, the system may qualify for streamlined regulatory pathways.

Limitations

Several limitations merit consideration:

1. Retrospective design: As a retrospective analysis of existing data, the study cannot directly assess the tool's impact on diagnostic timelines or patient outcomes.

2. TCGA cohort characteristics: TCGA samples may not fully represent the spectrum of disease encountered in routine clinical practice, particularly regarding early-stage or atypical presentations.

3. Missing data modalities: The current model does not incorporate radiological features or circulating biomarkers that might enhance performance.

4. Exclusion of bone sarcomas: The present study focused solely on soft tissue sarcomas, limiting generalizability to other sarcoma types.

5. Limited validation cohort diversity: While the control group included multiple cancer types, it did not include benign soft tissue tumors or inflammatory conditions that might mimic sarcoma.

Future Directions

Our research roadmap includes:

1. Expansion to bone sarcomas through partnerships with pediatric oncology centers,

2. Prospective validation in clinical settings with pre-diagnostic samples,

3. Integration of radiological features through deep learning approaches,

4. Exploration of circulating biomarkers to enhance detection sensitivity,

5. Development of explainable AI components to support clinical decision-making.

Conclusions

Our clinical–genomic risk assessment tool achieved robust stage-spanning detection of soft tissue sarcoma in TCGA cohorts with perfect specificity, supporting its feasibility for clinical decision support workflows. The moderate sensitivity (45.9%) represents

a meaningful advance for a condition currently characterized by significant diagnostic delays and could be further enhanced through incorporation of additional data modalities. The tool's stage-independent performance suggests potential utility for earlier detection scenarios where current approaches are limited. These findings support advancement to prospective clinical validation studies.

Author Contributions

Tiara Jamison conceived the study, engineered data pipelines, developed and validated the model, and wrote the manuscript.

Data Availability Statement

TCGA data are publicly available at https://portal.gdc.cancer.gov; GTEx data via https://gtexportal.org. The analysis code framework is available upon reasonable request for research purposes. The proprietary components of the algorithm are available for validation studies under appropriate data use agreements.

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