INPLASY

The Prognostic Value of Circulating Tumor Cells in Sarcoma: A Systematic Review and Meta-Analysis

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ADMINISTRATIVE INFORMATION

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Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 7 March 2026 and was last updated on 7 March 2026.

INTRODUCTION

R*eview question / Objective* Objective: To systematically evaluate the prognostic value of circulating tumor cells (CTCs) in patients with sarcoma.

PICOS framework:

Population: Patients diagnosed with any type of sarcoma (e.g., osteosarcoma, Ewing sarcoma, soft tissue sarcoma).

Index prognostic factor: Detection of circulating tumor cells (CTCs) in peripheral blood, detected by any method (e.g., CellSearch, RT-PCR, immunofluorescence) at baseline or during treatment.

Comparator: Not applicable (or patients with negative CTC detection).

Outcomes: Overall survival (OS), progression-free survival (PFS), or disease-specific survival (DSS).

Hazard ratios (HRs) with 95% confidence intervals (CIs) will be extracted or estimated.

Study design: Prospective cohort studies.

Rationale Sarcomas are a rare and heterogeneous group of malignant tumors with poor prognosis. While circulating tumor cells (CTCs) have shown prognostic value in common carcinomas (e.g., breast, colon cancer), their role in sarcomas remains unclear due to the rarity of the disease. Existing primary studies on CTCs in sarcoma are limited by small sample sizes and inconsistent results, making it difficult to draw definitive conclusions. Therefore, a systematic review and meta-analysis is needed to synthesize the available evidence, quantify the prognostic accuracy or association of CTCs with survival outcomes, and inform future research directions and clinical decision-making.

Condition being studied Sarcoma refers to a diverse group of malignant tumors that arise from mesenchymal tissues, such as bone, muscle, fat,

and cartilage. It comprises various subtypes, including osteosarcoma, Ewing sarcoma, and soft tissue sarcomas. Sarcomas are rare, accounting for approximately 1% of all adult malignancies and 15% of pediatric cancers. Despite multimodal treatment approaches including surgery, chemotherapy, and radiotherapy, the prognosis for patients with advanced or metastatic sarcoma remains poor, with high rates of recurrence and mortality. Identifying reliable prognostic biomarkers is crucial for risk stratification and personalized treatment.

METHODS

Search strategy Search strategy:

We will conduct a systematic search in the following electronic databases: PubMed, Embase, Medline, The Cochrane Library, and Web of Science. The search will be performed from the inception dates of these databases to December 2025.

A combination of Medical Subject Headings (MeSH) and free-text terms will be used to ensure search sensitivity and specificity. The MeSH terms applied will include "Sarcoma" and "Neoplastic Cells, Circulating". The free-text search terms will include: Sarcoma*, Circulating Tumor Cell*, CTCs.

The detailed search strategy for PubMed (which will be adapted for other databases) is as follows:

Search Query
#1 "Sarcoma"[Mesh] OR sarcoma*[Title/Abstract]
#2 "Neoplastic Cells, Circulating"[Mesh] OR "Circulating Tumor Cell*"[Title/Abstract] OR CTC[Title/Abstract] OR CTCs[Title/Abstract]
#3 #1 AND #2
To maximize the retrieval of relevant studies, no language restrictions will be applied. The search will be limited to article type of clinical research papers (e.g., clini

Participant or population Patients diagnosed with any type of sarcoma (including osteosarcoma, Ewing sarcoma, chondrosarcoma, and all subtypes of soft tissue sarcoma), confirmed by histopathological examination. No restrictions on age, gender, disease stage, or treatment regimen will be applied.

Intervention Not applicable for prognostic factor reviews. Instead, this section should describe the index prognostic factor:

Detection of circulating tumor cells (CTCs) in peripheral blood samples. Eligible studies must report CTC detection results using any validated method, including:

Marker-dependent methods: CellSearch system, CanPatrol, RT-PCR for tumor-specific markers

Marker-independent methods: ISET (isolation by size of epithelial tumor cells), other size-based filtration techniques

RNA-based detection methods

Both baseline CTC status (positive vs. negative, or high vs. low count) and longitudinal dynamic changes (clearance, persistence, increase, or decrease during/after treatment) will be considered.

Comparator For studies assessing baseline CTC status as a prognostic factor:

Comparator group: Patients with negative CTC detection or low CTC count

For studies assessing dynamic changes in CTCs:

Comparator group: Patients with favorable CTC dynamics (e.g., clearance from positive to negative, or decrease in count)

Experimental group: Patients with unfavorable CTC dynamics (e.g., persistence of positivity, increase in count, or emergence of new CTCs).

Study designs to be included Prospective or retrospective cohort studies that:Enrolled patients with histologically confirmed sarcomaAssessed CTCs in peripheral blood samplesReported the association between CTC status (baseline or dynamic) and clinical outcomesProvided sufficient data to extract or estimate effect sizes (HRs/RRs with 95% CIs).

Eligibility criteria Inclusion criteria:

Study design: Cohort studies (prospective or retrospective)

Population: Patients with histologically confirmed sarcoma

Exposure: Assessment of CTCs in peripheral blood

Outcomes: Reported association between CTCs and survival outcomes or metastasis

Data: Sufficient data to extract or calculate effect sizes

Exclusion criteria:

Case reports, case series (n<10), reviews, editorials, conference abstracts without full data

Studies not reporting original data

Studies not based on CTC count or dynamics

Duplicate publications.

Information sources Electronic databases:

PubMed (MEDLINE)

Embase

The Cochrane Library

Web of Science

Other sources:

Reference lists of included studies and relevant reviews

Clinical trial registries (if applicable).

Main outcome(s) The primary outcomes of this systematic review are survival outcomes associated with circulating tumor cell (CTC) status in sarcoma patients.

1. Progression-free survival (PFS)

Definition: Time from diagnosis, treatment initiation, or CTC assessment to disease progression (local recurrence, distant metastasis) or death from any cause, whichever occurs first.

Effect measure: Hazard ratio (HR) with 95% confidence interval (CI), comparing patients with positive/high CTC count vs. negative/low CTC count, or patients with unfavorable CTC dynamics vs. favorable dynamics.

2. Disease-free survival (DFS)

Definition: Time from definitive treatment (e.g., surgery) to disease recurrence or death from any cause.

Effect measure: Hazard ratio (HR) with 95% confidence interval (CI).

3. Overall survival (OS) (if reported in included studies)

Definition: Time from diagnosis or treatment to death from any cause.

Effect measure: Hazard ratio (HR) with 95% confidence interval (CI).

For studies reporting time-to-event ou.

Additional outcome(s) Secondary outcomes include:

1. Metastasis occurrence

Definition: Development of distant metastases during follow-up period.

Effect measure: Risk ratio (RR) with 95% confidence interval (CI), comparing patients with unfavorable CTC status vs. favorable CTC status.

Data source: Extracted from contingency tables (2×2 tables) or calculated from reported proportions.

2. Treatment response (if reported)

Definition: Response to neoadjuvant or adjuvant therapy, typically categorized as responders (complete or partial response) vs. non-responders (stable or progressive disease).

Effect measure: Odds ratio (OR) or risk ratio (RR) with 95% CI.

3. Dynamic changes in CTCs

We will specifically analyze studies that report longitudinal CTC assessments, categorizing patients into:

Favorable dynamics: CTC clearance (positive to negative), decrease in count, or persistently negative

Unfavorable dynamics: CTC persistence (positive remains positive), increase in count, or emergence of new CTCs

The association between.

Data management 1. Reference management software
All retrieved records from database searches will be imported into EndNote X9 (Clarivate Analytics) for literature management. Duplicate records will

be identified and removed using EndNote's duplicate identification function, followed by manual verification.

2. Screening process

Title and abstract screening: Two reviewers (KX Xie, C Zhou) will independently screen all titles and abstracts against the pre-defined eligibility criteria. Records that clearly do not meet the inclusion criteria will be excluded. For records with insufficient information to make a decision, they will be carried forward to full-text review.

Full-text screening: The same two reviewers will independently assess full texts of potentially eligible studies. Reasons for exclusion at this stage will be documented and reported in the PRISMA flow diagram.

Disagreement resolution: Any disagreements between the two reviewers at any stage of screening will be resolved through discussion. If consensus cannot.

Quality assessment / Risk of bias analysis Due to the limited number of included studies and the exploratory nature of this review, a formal risk of bias assessment using standardized tools (e.g., QUIPS for prognostic studies) may not be feasible. Instead, the following methodological quality indicators will be assessed:

Clear definition of CTC positivity threshold

Blinding of outcome assessment

Completeness of follow-up data

Adjustment for potential confounders

Direct reporting of HRs vs. estimation from survival curves

These factors will be considered in sensitivity analyses and discussed as limitations.

Strategy of data synthesis Meta-analysis:

A random-effects model will be used for all meta-analyses to account for anticipated clinical and methodological heterogeneity

For time-to-event outcomes, pooled HRs with 95% CIs will be calculated using the inverse variance method

For dichotomous outcomes, pooled RRs with 95% CIs will be calculated

Statistical significance will be set at $P < 0.05$

Heterogeneity assessment:

Statistical heterogeneity will be quantified using the I^2 statistic

I^2 values of 25%, 50%, and 75% will be considered low, moderate, and high heterogeneity, respectively

The Cochran Q test will be performed, with $P < 0.10$ indicating significant heterogeneity

Subgroup and sensitivity analyses:

If sufficient studies are available, subgroup analyses will be performed based on:

Sarcoma type (bone vs. soft tissue sarcoma)

CTC detection method (marker-dependent vs. marker-independent)

Timing of CTC assessment (baseline vs. post-treatment)

Sensitivity analyses will be conducted by:

Excluding studies where HRs were estimated from survival curves

Excluding studies with high risk of bias

Using fixed-effects models to test the robustness of findings.

Subgroup analysis No subgroup analyses are planned due to the anticipated limited number of eligible studies.

Sarcoma is a rare malignancy, and research on circulating tumor cells (CTCs) in sarcoma patients is still in its early stages. Based on preliminary literature scoping, we expect a small number of eligible studies (likely fewer than 10), which will be insufficient for meaningful statistical subgroup analyses.

If sufficient studies become available (which is unlikely given the rarity of the condition), the following subgroup analyses would be considered exploratory:

By sarcoma type (bone vs. soft tissue sarcoma)

By CTC detection method (marker-dependent vs. marker-independent)

However, given the expected small evidence base, these analyses will not be formally conducted. Instead, any observed heterogeneity will be explored descriptively in the discussion.

Sensitivity analysis To assess the robustness of the pooled effect estimates, the following sensitivity analyses will be conducted:

1. Influence of individual studies

Leave-one-out analysis: The meta-analysis will be repeated after sequentially omitting each study to assess whether any single study disproportionately influences the pooled effect estimate.

Studies with extreme effect sizes or large weights will be examined more closely.

2. Methodological quality

Analysis restricted to studies with direct reporting of HRs (excluding studies where HRs were estimated from survival curves)

Rationale: Estimated HRs may introduce measurement error and bias.

3. Statistical model

Fixed-effects model will be applied to compare results with the random-effects model

If results are consistent across models, this increases confidence in the findings.

4. Outlier identification

Studies identified as statistical outliers (based on Galbraith plots or influence diagnostics) will be excluded in a sensitivity analysis to assess their impac.

Language restriction No language restrictions will be applied.

Country(ies) involved China.

Keywords Sarcoma ; Circulating Tumor Cells ; Prognosis ; Liquid Biopsy ; Meta-Analysis.

Contributions of each author
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