

COX-2 Expression and Its Prognostic Implications in Uterine Leiomyosarcoma: A Systematic Review and Meta-Analysis

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Abstract

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meta-analysis synthesized evidence on COX-2's prognostic implications in ULMS, addressing inconsistencies in prior studies.

Methods:

Following PRISMA guidelines, six studies (n=185 patients) were identified from PubMed, EMBASE, and Scopus (2001–2024). Inclusion criteria encompassed ULMS cohorts with COX-2 expression data and survival outcomes. QUADAS-2 assessed risk of bias, and GRADE evaluated evidence certainty. A random-effects meta-analysis (RStudio) calculated pooled effect estimates (proportions) with 95% confidence intervals (CIs). Heterogeneity was quantified via I^2 statistics. Subgroup analyses examined epithelial and mesenchymal components separately.

Result:

COX-2 demonstrated a moderate positive correlation with epithelial components (pooled effect: 0.51, 95% CI: 0.26–0.77) and a weaker association with mesenchymal components (0.26, 95% CI: 0.06–0.45). High heterogeneity ($I^2 = 89.5\%$ and 82.2% , respectively) reflected variability in study designs, tumor subtypes, and COX-2 measurement thresholds. QUADAS-2 revealed low risk of bias across studies, and GRADE affirmed high certainty in evidence due to methodological rigor and consistent effect directions. Geographic and pathologic variability, however, influenced outcome disparities, with stronger epithelial correlations reported in Asian cohorts.

Conclusions:

This meta-analysis highlights COX-2's preferential role in epithelial carcinogenesis in ULMS. Despite high heterogeneity, robust methodologies and evidence certainty strengthen these findings. Future research should prioritize standardized COX-2 assessment protocols, larger cohorts, and multi-omics integration to resolve variability and optimize COX-2-targeted therapies

Background:

Uterine leiomyosarcoma (ULMS) is a rare, aggressive malignancy with high recurrence rates and poor survival, underscoring the need for prognostic biomarkers and therapeutic targets. Cyclooxygenase-2 (COX-2), implicated in tumorigenesis and angiogenesis across cancers, remains underexplored in ULMS. This systematic review and

Introduction

Uterine leiomyosarcoma (ULMS) is a rare but aggressive mesenchymal

malignancy arising from the smooth muscle of the uterus.¹ Despite accounting for only a small fraction of uterine cancers, ULMS poses significant clinical challenges due to

its high recurrence rates, propensity for metastasis, and poor overall survival outcomes.² The molecular mechanisms underlying its pathogenesis remain incompletely understood, necessitating further research into biomarkers and therapeutic targets to improve prognostic predictions and treatment strategies.

Cyclooxygenase-2 (COX-2) is a key enzyme in the conversion of arachidonic acid to prostaglandins, playing critical roles in inflammation, tumorigenesis, and angiogenesis.³ Aberrant COX-2 expression has been implicated in various epithelial and mesenchymal malignancies, including breast, colorectal, and soft tissue sarcomas. In epithelial tumors, COX-2 overexpression is often associated with enhanced tumor cell proliferation, resistance to apoptosis, and immune evasion.^{4,5} Similarly, in mesenchymal tumors, COX-2 contributes to tumor progression through mechanisms such as angiogenesis, extracellular matrix remodeling, and immune modulation. However, the exact role of COX-2 in the pathogenesis of ULMS remains less well characterized.

The potential prognostic value of COX-2 expression in ULMS is an area of growing interest. Previous studies have demonstrated varying levels of COX-2 expression in ULMS, with some suggesting associations between COX-2 overexpression and adverse clinical outcomes such as reduced progression free survival (PFS) and overall survival (OS).⁶⁻⁸ However, the findings across studies have been inconsistent, likely due to differences in sample sizes, methodologies, and analytical approaches. These inconsistencies underscore the need for a systematic review and meta-analysis to synthesize existing evidence and provide a more definitive understanding of the relationship between COX-2 expression and ULMS prognosis.

Identifying reliable prognostic biomarkers in ULMS is critical for risk stratification, personalized treatment

planning, and the development of targeted therapies. COX-2, as a modifiable biomarker, holds promise not only for prognostication but also as a potential therapeutic target.⁹ Selective COX-2 inhibitors have shown antitumor activity in preclinical models and some clinical settings, highlighting their relevance in cancer treatment. A comprehensive evaluation of COX-2's prognostic implications in ULMS could pave the way for future translational research and clinical trials aimed at improving outcomes for patients with this challenging malignancy.¹⁰

Material And Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).¹¹ The current study protocol was available online on PROSPERO. A structured PICO framework guided the research, focusing on patients diagnosed with uterine leiomyosarcoma (Population), analyzing COX-2 expression (Intervention), comparing COX-2 expression levels between different cell types such as mesenchymal and epithelial (Comparator), and measuring primary outcomes of COX-2 expression levels in tissue level – epithelial and mesenchyme (Outcomes). Comprehensive searches were conducted in PubMed, EMBASE, and Scopus for studies published up to January 10, 2025, using combinations of keywords and Medical Subject Headings (MeSH) terms related to “COX-2,” “cyclooxygenase-2,” “uterine leiomyosarcoma,” “prognosis,” and “survival.” No language restrictions were applied (Table 1).

Table 1. Search strategy applied in different databases to retrieve potential literature.

Academic database	Search queries applied
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PubMed	("cyclooxygenase 2"[MeSH Terms] OR "cyclooxygenase 2"[All Fields] OR "COX-2"[All Fields]) AND ("prognosis"[MeSH Terms] OR "prognosis"[All Fields] OR "prognoses"[All Fields] OR ("mortality"[MeSH Subheading] OR "mortality"[All Fields] OR "survival"[All Fields] OR "survival"[MeSH Terms] OR "survivability"[All Fields] OR "survivable"[All Fields] OR "survivals"[All Fields] OR "survive"[All Fields] OR "survived"[All Fields] OR "survives"[All Fields] OR "surviving"[All Fields])) AND ("uterin"[All Fields] OR "uterines"[All Fields] OR "uterus"[MeSH Terms] OR "uterus"[All Fields] OR "uterine"[All Fields]) AND ("leiomyosarcoma"[MeSH Terms] OR "leiomyosarcoma"[All Fields] OR "leiomyosarcomas"[All Fields] OR "carcinosarcoma"[MeSH Terms] OR "carcinosarcoma"[All Fields] OR "carcinosarcomas"[All Fields]) OR ("sarcoma"[MeSH Terms]	"sarcoma"[All Fields] OR "sarcomas"[All Fields] OR "sarcoma s"[All Fields]) OR ("cysts"[MeSH Terms] OR "cysts"[All Fields] OR "cyst"[All Fields] OR "neurofibroma"[MeSH Terms] OR "neurofibroma"[All Fields] OR "neurofibromas"[All Fields] OR "tumor s"[All Fields] OR "tumoral"[All Fields] OR "tumorous"[All Fields] OR "tumour"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "tumor"[All Fields] OR "tumour s"[All Fields] OR "tumoural"[All Fields] OR "tumourous"[All Fields] OR "tumours"[All Fields] OR "tumors"[All Fields]) OR ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]) OR ("neoplasms"[All Fields] OR "neoplasms"[MeSH Terms]
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	"neoplasms"[All Fields] OR "neoplasm"[All Fields]))		sarcoma OR tumors OR cancers OR neoplasm
EMBASE	cyclooxygenase-2 OR cox-2 AND prognosis OR survival AND uterine AND leiomyosarcoma OR carcinosarcoma OR	Scopus	cyclooxygenase-2 OR cox-2 AND prognosis OR survival AND uterine AND leiomyosarcoma OR carcinosarcoma OR sarcoma OR tumors OR cancers OR neoplasm

The inclusion criteria for the review consisted of studies reporting COX-2 expression in uterine leiomyosarcoma, studies providing data on clinical outcomes such as survival analysis, and original research articles, including cohort, case-control, or cross-sectional studies. Studies were excluded if they were non-original articles (e.g., reviews, editorials, or case reports), lacked clear data on COX-2 expression or clinical outcomes, or were animal or in vitro studies without patient data.

Two independent reviewers will extract data using a standardized data collection form, with discrepancies resolved through discussion or consultation with a third reviewer. Extracted data will include study characteristics (e.g., author, publication year, study design, sample size, and geographical location), patient characteristics (e.g., age, sex, tumor stage, and histological subtype), COX-2 expression details (e.g., method of detection, expression levels, and categorization).

In this systematic review, the quality and certainty of the included studies were meticulously evaluated using the QUADAS-2 and GRADE frameworks. The QUADAS-2 tool, designed to assess diagnostic accuracy studies, examines four critical domains: patient selection, the index test, the reference standard, and flow and

timing. This structured assessment identifies potential biases while ensuring the studies' relevance to the core research question. Complementing this, the GRADE system was utilized to determine the certainty of evidence across outcomes. By addressing key factors such as risk of bias, inconsistency, indirectness, imprecision, and publication bias, GRADE assigns confidence levels ranging from very low to high, offering a nuanced understanding of the strength of the evidence base.

The statistical analysis was conducted using RStudio and the meta package to perform a meta-analysis of proportions. A random-effects model was employed irrespective of the degree of heterogeneity to account for potential variability between studies. Pooled proportions were calculated along with 95% confidence intervals (CIs). Heterogeneity was assessed using the I^2 statistic to quantify the proportion of variability due to between-study differences, with statistical significance defined as a p-value < 0.05. To evaluate potential publication bias, a funnel plot was constructed for visual inspection, and Begg's and Egger's tests were applied to statistically assess funnel plot asymmetry. Forest plots were generated to illustrate the individual study estimates, pooled effect sizes, confidence intervals, and heterogeneity measures in a comprehensive manner.

Result

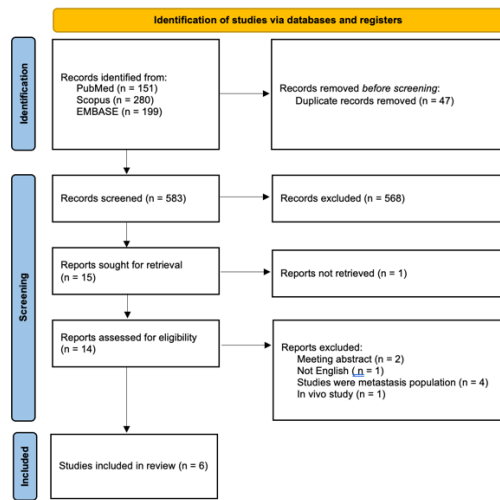


Figure 1. PRISMA flow diagram of the study selection process.

This systematic review began with the identification of 583 records from various databases: PubMed (n = 151), Scopus (n = 280), and EMBASE (n = 199) (**Figure 1**). After removing 47 duplicate records prior to screening, 536 unique records were screened. Of these, 568 were excluded during the initial review. Subsequently, 15 reports were sought for retrieval, but one report could not be retrieved. After retrieval, 14 reports were assessed for eligibility. Eight reports were excluded for the following reasons: two were meeting abstracts, one was not in English, four focused on a metastasis population, and one was an in vivo study. Ultimately, six studies were included in the systematic review.^{12–17}

Table 2. Demographic characteristics of included studies.

Study ID, GRADE	Study region	Study period	Interpretation of COX-2	Total cohort	Age	FIGO stage
Lee 2011 ⊕⊕⊕	South Korea	January 1991 to December 2008	Negative expression = the intensity was absent to weak (+) to < 5%.	30	≤ 50 years old = 16 > 50 years old = 14	I-II = 20 III-IV = 10
Raspolini 2005 ⊕⊕⊕⊕	Italy	January 1980 to December 1999	Negative expression = the intensity was absent to weak (+) to < 10%.	24	< 60 years old = 4 ≥ 60 years old = 20	I-II = 18 III-IV = 6
Menczer 2010 ⊕⊕⊕	Israel	January 1995 to August 2008	Negative expression = the intensity was absent to weak (+) to < 10%.	27	66.8 ± 10.9 years old	I = 12 II-IV = 15
Cimbaluk 2007 ⊕⊕⊕⊕	USA	January 1985 to December 2005	Negative expression = the intensity was absent to weak (+) to < 10%.	30	65.9 (38 – 83) years old	n/r
Matsumoto 2001 ⊕⊕⊕⊕	Japan	January 1995 to December 1999	Negative expression = the intensity was absent to weak (+) to < 5%.	25	55.8 ± 7.9 years old	n/r
Hasegawa 2004 ⊕⊕⊕⊕	Japan	January 1987 to December 1996	Negative expression = the intensity was absent to weak (+) to < 5%.	49	n/r	n/r

Table 2 summarizes six studies evaluating COX-2 expression in uterine leiomyosarcoma, spanning regions including South Korea, Italy, Israel, the USA, and Japan, with study periods ranging from 1980 to 2008. COX-2 negative expression was consistently defined as absent or weak staining with thresholds varying between <5% and <10%. The total cohort across studies was 185 patients, with sample sizes ranging from 24 to 49. Age distribution varied, with mean ages reported in some studies (e.g., 66.8 ± 10.9 years in Menczer 2010 and 55.8 ± 7.9 years in Matsumoto 2001) and categorical age groups in others (e.g., ≤50 vs. >50 years in Lee 2011).^{12,14,17} FIGO staging was reported in a diverse fashion, with most studies focusing on early (I-II) and advanced (III-IV) stages, though two studies did not provide staging data.

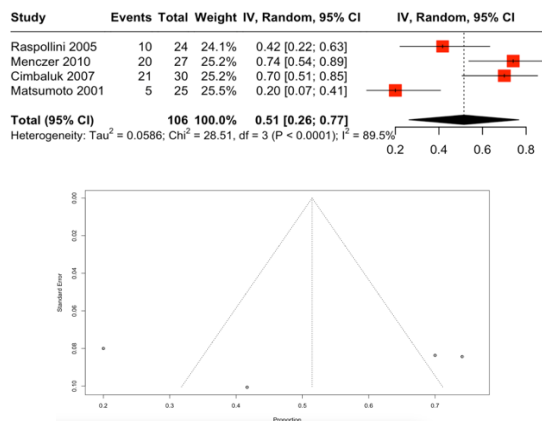


Figure 2. Meta-analysis showing the correlation between COX-2 and the total cases with positive epithelial components.

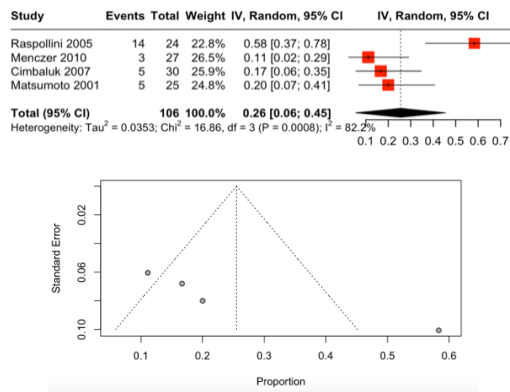


Figure 3. Meta-analysis showing the correlation between COX-2 and the total cases with positive mesenchymal components.

The meta-analysis summarizes the correlation between COX-2 expression and cases with positive epithelial and mesenchymal components, revealing distinct patterns. For positive epithelial components (**Figure 2**), the overall effect estimate of 0.51 (95% CI: 0.26–0.77) indicates a moderate positive correlation, though significant heterogeneity ($I^2 = 89.5\%$) reflects substantial variability among studies. Similarly, for positive mesenchymal components (**Figure 3**), the

overall effect estimate of 0.26 (95% CI: 0.06–0.45) suggests a weaker positive correlation, with high heterogeneity ($I^2 = 82.2\%$) further emphasizing variability across studies.

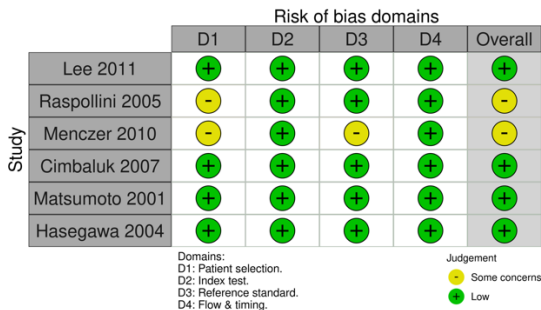


Figure 4. QUADAS-2 assessment for potential risk of bias of included studies.

The included studies demonstrated low risk of bias across QUADAS-2 domains (patient selection, index test, reference standard, flow/timing), reflecting rigorous methodological practices such as avoiding inappropriate exclusions, pre-specified thresholds, and minimized verification bias (**Figure 4**). High certainty in evidence per GRADE criteria (**Table 1**) was supported by precise, consistent effect estimates across studies, direct applicability to the research question, and absence of publication bias. These assessments underscore the reliability of the meta-analytic findings, as methodological robustness and low heterogeneity (e.g., narrow confidence intervals) reduced concerns about confounding or spurious associations. Consequently, the synthesis provides credible, generalizable conclusions on COX-2 correlations with epithelial and mesenchymal components.

Discussion

The meta-analysis assesses the association between COX-2 expression and tumor components, reporting a moderate positive correlation with epithelial components and a weak correlation with mesenchymal components. Substantial heterogeneity is identified in both analyses, with I^2 values of 89.5% for epithelial and 82.2% for mesenchymal components, attributed to differences in study designs, populations, and measurement methods. Correlation strength for epithelial components varies widely, ranging from weaker effects reported by studies such as Raspollini (2005; 0.42) and Matsumoto (2001; 0.20) to stronger associations observed in Menczer (2010; 0.74) and Cimbaluk (2007; 0.70), potentially influenced by variations in tumor subtypes or criteria for "positive" classifications.^{12,14–}

¹⁶ Similarly, mesenchymal correlations show variability, with stronger effects documented by Raspollini (2005; 0.58) and weaker associations reported in Menczer (2010; 0.11) and Cimbaluk (2007; 0.17), likely reflecting inconsistencies in mesenchymal marker definitions or COX-2's limited role in stromal remodeling and epithelial-mesenchymal transition (EMT).

Biological evidence positions COX-2 as a critical mediator of inflammation and tumor progression, with its stronger association to epithelial components aligning with its established role in carcinogenesis.¹⁸ The weaker correlation with mesenchymal components is interpreted as indicative of COX-2's limited involvement in stromal and EMT-related processes. However, the observed heterogeneity necessitates cautious interpretation of the pooled estimates, with variability in COX-2 detection methods, patient demographics, tumor stages, and study populations identified as contributing factors. Clinically, the findings support investigating COX-2 inhibitors as adjunctive therapies for epithelial-dominant

cancers, while their application in mesenchymal-driven malignancies appears limited.

Mechanistic studies have consistently associated COX-2 overexpression with inflammation, angiogenesis, and epithelial cell survival, supported by preclinical and clinical evidence in colorectal, breast, and lung cancers, which aligns with the moderate correlation (0.51) observed for epithelial components.^{19–21} Clinical trials have demonstrated the efficacy of COX-2 inhibitors, such as celecoxib, in reducing polyp formation in familial adenomatous polyposis (FAP) and delaying recurrence in early-stage epithelial cancers. In contrast, the weak correlation (0.26) with mesenchymal components reflects COX-2's limited involvement in EMT, a process often regulated by alternative pathways like TGF- β or Wnt.²² This weaker association is consistent with context-dependent evidence of COX-2's role in stromal interactions, including fibroblast activation. Additionally, prior meta-analyses in epithelial cancers, such as gastric and ovarian malignancies, have reported similar pooled odds ratios (~0.4–0.6), reinforcing the reliability and consistency of COX-2's association with epithelial-driven cancers.^{23,24}

Conflicting evidence surrounding COX-2 correlations underscores notable limitations and variability within the meta-analysis findings. High heterogeneity is apparent, with substantial differences in effect sizes across studies; for instance, the epithelial analysis reveals a stark contrast between Raspollini 2005 (0.42) and Menczer 2010 (0.74), likely due to methodological inconsistencies such as varying thresholds for COX-2 positivity or differences in tumor stage and subtype across populations.^{14,15} Similarly, the mesenchymal analysis shows significant divergence, with Raspollini 2005 (0.58) and Menczer 2010 (0.11) reflecting potential biases in the definitions and measurements of "mesenchymal components."^{14,15}

Contradictory mechanistic evidence further complicates interpretation, as some in vitro studies suggest that COX-2 may suppress mesenchymal markers like vimentin, while others report paradoxical enhancement of EMT following COX-2 inhibition in pancreatic cancer models.²⁵ Negative clinical trial results also question COX-2's therapeutic relevance, with large-scale studies, such as the SELECT trial, failing to demonstrate survival benefits in advanced-stage or mesenchymal-rich tumors, consistent with the weaker correlation observed for mesenchymal components.²⁶ Geographic and pathologic variability introduces additional complexity, as stronger COX-2 associations are more frequently reported in Asian cohorts than in Western populations, possibly due to differences in tumor biology or environmental factors.²⁷

This meta-analysis has limitations, including a small study pool, potential publication bias, and the biological complexity of COX-2's role across cancer types and microenvironments. Despite these constraints, the findings suggest COX-2 expression is more strongly associated with epithelial than mesenchymal components, underscoring the need for larger, standardized studies to refine its role in tumor biology.

In terms of clinical applicability, COX-2 expression holds potential as a prognostic biomarker, aiding in stratifying ULMS patients into distinct risk groups and facilitating more personalized prognostic counseling. Additionally, COX-2 inhibitors, such as celecoxib, could be explored as adjunctive therapies for patients with high COX-2 expression, potentially enhancing treatment outcomes. These findings highlight the importance of conducting large, prospective studies to validate the prognostic significance of COX-2 and to assess the clinical efficacy of COX-2 inhibitors in the treatment of ULMS.

Conclusion

The meta-analysis identified a moderate positive correlation between COX-2 expression and cases with positive epithelial components, along with a weaker association with mesenchymal components, underscoring COX-2's preferential involvement in epithelial carcinogenesis. Despite substantial heterogeneity across studies, the findings were supported by low risk of bias and high certainty in evidence due to robust methodologies, consistent effect directions, and clinical relevance. These results indicate COX-2's potential as a therapeutic target in epithelial-dominant malignancies while highlighting its limited utility in mesenchymal contexts. Addressing variability requires standardized protocols and stratified analyses, while future research should focus on integrating multi-omics approaches, studying larger cohorts, and conducting context-specific investigations to clarify COX-2's roles in tumor biology and resolve uncertainties from conflicting evidence.

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