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

Levita Dyah Kartika Suherman[1], Kenny Sungkarto[2], Devanti Octavia Ellyamurti[3], Tiara Namora Tarigan, Puspa Negara[4], Teddy Tjahyanto[5], Jeremiah Hilkiah Wijaya[6]

[1]Universitas Airlangga, Surabaya, Indonesia
[2]Faculty of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia
[3]Master of Hospital Administration, University of Pelita Harapan, Lippo Karawaci, Tangerang, Indonesia 15811
[4]Faculty of Medicine and Health Sciences, Krida Wacana Christian University, Jakarta, Indonesia
[5]Tarumanagara University, Jakarta, Indonesia
[6]Department of Medicine, University of Pelita Harapan, Lippo Karawaci, Tangerang, Indonesia 15811

Citation : Suherman LD, Sungkarto K, Ellyamurti DO, et al. COX-2 Expression and Its Prognostic Implications in Uterine Leiomyosarcoma: A Systematic Review and Meta-Analysis. Medicinus. 2025 February; 14(2): 113-123.
Keywords: Cyclooxygenase-2; Epithelial-mesenchymal components; Prognostic biomarker; Uterine leiomyosarcoma
Correspondance : Levita Dyah Kartika Suherman
E-mail : vitadyahkartika@gmail.com
Online First : February 2025

Abstract

Background : Uterine leiomyosarcoma (ULMS) is a rare, aggressive malignancy with high recurrence and poor survival, necessitating prognostic biomarkers and therapeutic targets. Cyclooxygenase-2 (COX-2), implicated in tumorigenesis and angiogenesis, remains understudied in ULMS. This systematic review and meta-analysis assessed COX-2's prognostic role in ULMS.

Methods : Following PRISMA guidelines, six studies (n=185) were retrieved from PubMed, EMBASE, and Scopus (2001–2024). Inclusion criteria required ULMS cohorts with COX-2 expression data and survival outcomes. Risk of bias was assessed using QUADAS-2, and evidence certainty via GRADE. A random-effects meta-analysis calculated pooled effect estimates with 95% confidence intervals (CIs), while heterogeneity was evaluated using I^2 statistics.\

Result : COX-2 expression correlated moderately with epithelial components (pooled effect: 0.51, 95% CI: 0.26–0.77) and weakly with mesenchymal components (0.26, 95% CI: 0.06–0.45). High heterogeneity (I^2 = 89.5% and 82.2%) reflected differences in study design, tumor subtypes, and COX-2 measurement thresholds. QUADAS-2 indicated a low risk of bias, and GRADE confirmed high evidence certainty. Stronger epithelial correlations were observed in Asian cohorts, highlighting geographic variability.
Conclusions: COX-2 plays a more significant role in epithelial-driven ULMS carcinogenesis. Despite heterogeneity, robust methodologies support these findings. Future studies should standardize COX-2 assessment, expand cohort sizes, and integrate multi-omics approaches to refine prognostic and therapeutic applications.

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
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] OR "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 ("neoplasm s"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "neoplasm"[All Fields]))
EMBASE	cyclooxygenase-2 OR cox-2 AND prognosis OR survival AND uterine AND leiomyosarcoma OR carcinosarcoma OR sarcoma OR tumors OR cancers OR neoplasm
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

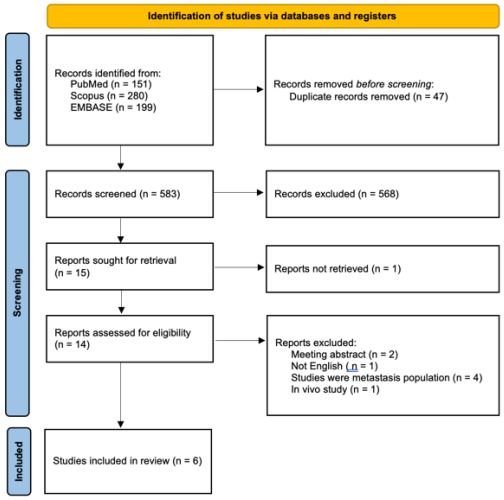

Figure 1. PRISMA flow diagram of the study selection process.

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
Raspollini 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.

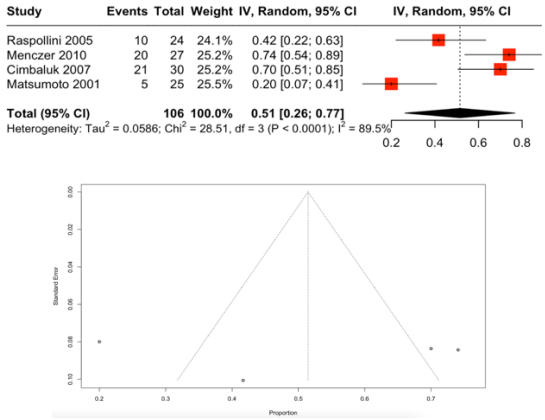

Figure 2. Meta-analysis showing the correlation between COX-2 and the total cases with positive epithelial components.

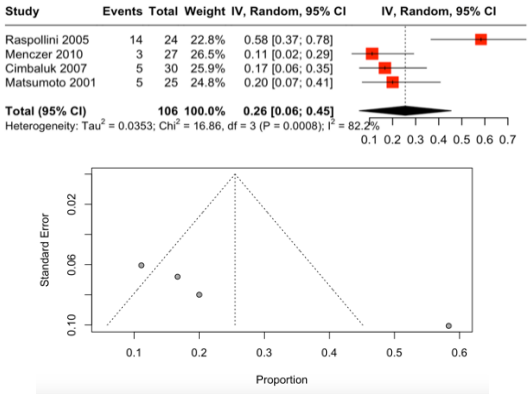

Figure 3. Meta-analysis showing the correlation between COX-2 and the total cases with positive mesenchymal components.

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 estimates 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 estimates 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.

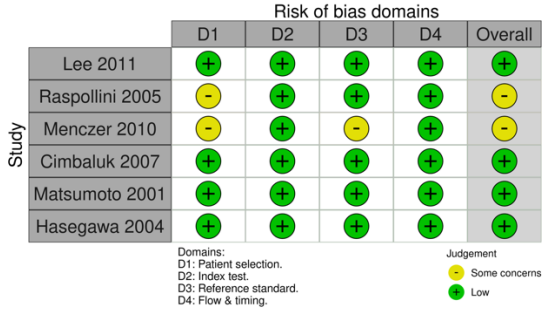

Figure 4. QUADAS-2 assessment for potential risk of bias of included studies.

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.

References

1. Dunphy L, Sheridan G. Uterine leiomyosarcoma: a rare clinical entity. BMJ Case Rep. 2021 Aug 25;14(8):e244233. https://doi.org/10.1136/bcr-2021-244233
2. Kerrison WGJ, Thway K, Jones RL, Huang PH. The biology and treatment of leiomyosarcomas. Critical Reviews in Oncology/Hematology. 2023 Apr;184:103955. https://doi.org/10.1016/j.critrevonc.2023.103955
3. Kuwano T, Nakao S, Yamamoto H, Tsuneyoshi M, Yamamoto T, Kuwano M, et al. Cyclooxygenase 2 is a key enzyme for inflammatory cytokine-induced angiogenesis. FASEB J. 2004 Feb;18(2):300–10. https://doi.org/10.1096/fj.03-0473com
4. Szweda M, Rychlik A, Babińska I, Pomianowski A. Significance of Cyclooxygenase-2 in Oncogenesis. J Vet Res. 2019 Jun;63(2):215–24. https://doi.org/10.2478/jvetres-2019-0030
5. Huang R, Yu J, Zhang B, Li X, Liu H, Wang Y. Emerging COX-2 inhibitors-based nanotherapeutics for cancer diagnosis and treatment. Biomaterials. 2025 Apr;315:122954. https://doi.org/10.1016/j.biomaterials.2024.122954
6. Du J, Feng J, Luo D, Peng L. Prognostic and Clinical Significance of COX-2 Overexpression in Laryngeal Cancer: A Meta-Analysis. Front Oncol. 2022;12:854946. https://doi.org/10.3389/fonc.2022.854946
7. Peng L, Zhou Y, Wang Y, Mou H, Zhao Q. Prognostic Significance of COX-2 Immunohistochemical Expression in Colorectal Cancer: A Meta-Analysis of the Literature. Aziz SA, editor. PLoS ONE. 2013 Mar 20;8(3):e58891. https://doi.org/10.1371/journal.pone.0058891
8. Hamy AS, Tury S, Wang X, Gao J, Pierga JY, Giacchetti S, et al. Celecoxib With Neoadjuvant Chemotherapy for Breast Cancer Might Worsen Outcomes Differentially by COX-2 Expression and ER Status: Exploratory Analysis of the REMAGUS02 Trial. J Clin Oncol. 2019 Mar 10;37(8):624–35. https://doi.org/10.1200/jco.18.00636
9. Guo J, Zheng J, Tong J. Potential Markers to Differentiate Uterine Leiomyosarcomas from Leiomyomas. Int J Med Sci. 2024;21(7):1227–40. https://doi.org/10.7150/ijms.93464

10. Ogino S, Kirkner GJ, Nosho K, Irahara N, Kure S, Shima K, et al. Cyclooxygenase-2 expression is an independent predictor of poor prognosis in colon cancer. Clin Cancer Res. 2008 Dec 15;14(24):8221–7. https://doi.org/10.1158/1078-0432.CCR-08-1841
11. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021 Mar 29; 372: n71. https://doi.org/10.1136/bmj.n71
12. Matsumoto Y, Ishiko O, Sumi T, Yoshida H, Deguchi M, Nakagawa E, et al. Cyclooxygenase-2 expression in malignant mesenchymal tumors and related uterine lesions. Oncol Rep. 2001;8(6):1225–7. https://doi.org/10.3892/or.8.6.1225
13. Hasegawa K, Ohashi Y, Ishikawa K, Yasue A, Kato R, Achiwa Y, et al. Expression of cyclooxygenase-2 in uterine endometrial cancer and anti-tumor effects of a selective COX-2 inhibitor. Int J Oncol. 2005 May;26(5):1419–28. https://doi.org/10.3892/ijo.26.5.1419
14. Menczer J, Schreiber L, Sukmanov O, Kravtsov V, Berger E, Golan A, et al. COX-2 expression in uterine carcinosarcoma. Acta Obstet Gynecol Scand. 2010;89(1):120–5. https://doi.org/10.3109/00016340903342006
15. Raspollini MR, Susini T, Amunni G, Paglierani M, Taddei A, Marchionni M, et al. COX-2, c-KIT and HER-2/neu expression in uterine carcinosarcomas: prognostic factors or potential markers for targeted therapies? Gynecol Oncol. 2005 Jan;96(1):159–67. https://doi.org/10.1016/j.ygyno.2004.09.050
16. Cimbaluk D, Rotmensch J, Scudiere J, Gown A, Bitterman P. Uterine carcinosarcoma: immunohistochemical studies on tissue microarrays with focus on potential therapeutic targets. Gynecol Oncol. 2007 Apr;105(1):138–44. https://doi.org/10.1016/j.ygyno.2006.11.001
17. Lee CH, Roh JW, Choi JS, Kang S, Park IA, Chung HH, et al. Cyclooxygenase-2 is an independent predictor of poor prognosis in uterine leiomyosarcomas. Int J Gynecol Cancer. 2011 May;21(4):668–72. https://doi.org/10.1097/igc.0b013e3182150d56
18. Esbona K, Yi Y, Saha S, Yu M, Van Doorn RR, Conklin MW, et al. The Presence of Cyclooxygenase 2, Tumor-Associated Macrophages, and Collagen Alignment as Prognostic Markers for Invasive Breast Carcinoma Patients. Am J Pathol. 2018 Mar;188(3):559–73. https://doi.org/10.1016/j.ajpath.2017.10.025
19. Dixon DA, Blanco FF, Bruno A, Patrignani P. Mechanistic aspects of COX-2 expression in colorectal neoplasia. Recent Results Cancer Res. 2013;191:7–37. https://doi.org/10.1007/978-3-642-30331-9_2
20. Wang D, Dubois RN. The role of COX-2 in intestinal inflammation and colorectal cancer. Oncogene. 2010 Feb 11;29(6):781–8. https://doi.org/10.1038/onc.2009.421

21. Jiang Q. Natural Forms of Vitamin E as Effective Agents for Cancer Prevention and Therapy. Advances in Nutrition. 2017 Nov;8(6):850–67. https://doi.org/10.3945/an.117.016329
22. Schuhwerk H, Brabletz T. Mutual regulation of TGFβ-induced oncogenic EMT, cell cycle progression and the DDR. Seminars in Cancer Biology. 2023 Dec;97:86–103. https://doi.org/10.1016/j.semcancer.2023.11.009
23. Sun H, Zhang X, Sun D, Jia X, Xu L, Qiao Y, et al. COX-2 expression in ovarian cancer: an updated meta-analysis. Oncotarget. 2017 Oct 20;8(50):88152–62. https://doi.org/10.18632/oncotarget.21538
24. Arora T, Mullangi S, Vadakekut ES, Lekkala MR. Epithelial Ovarian Cancer. StatPearls Publishing. 2025. http://www.ncbi.nlm.nih.gov/books/NBK567760/
25. Liao TT, Yang MH. Revisiting epithelial-mesenchymal transition in cancer metastasis: the connection between epithelial plasticity and stemness. Mol Oncol. 2017 Jul;11(7):792–804. https://doi.org/10.1002/1878-0261.12096
26. Doll CM, Winter K, Gaffney DK, Ryu JK, Jhingran A, Dicker AP, et al. COX-2 Expression and Survival in Patients with Locally Advanced Cervical Cancer Treated With Chemoradiotherapy and Celecoxib. International Journal of Gynecological Cancer. 2013 Jan;23(1):176–83. https://doi.org/10.1097/igc.0b013e3182791efc
27. Shin WS, Xie F, Chen B, Yu P, Yu J, To KF, et al. Updated Epidemiology of Gastric Cancer in Asia: Decreased Incidence but Still a Big Challenge. Cancers (Basel). 2023 May 6;15(9):2639. https://doi.org/10.3390/cancers15092639

Author's Statement

The authors declare that all images, figures, and content in this manuscript are the authors' original work or have obtained the necessary permissions for reuse from the respective authors and publishers of the referenced materials.

(Levita Dyah Kartika Suherman)