e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(1); 1372-1376

Original Research Article

Meta-Analysis of Immunohistochemical Markers for Differentiating Benign and Malignant Mesenchymal Tumors

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Received: 28-11-2025 / Revised: 27-12-2025 / Accepted: 29-01-2026

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Conflict of interest: Nil

Abstract:

Background: Mesenchymal tumors include a diverse range of benign and malignant neoplasms exhibiting overlapping histomorphological characteristics. Precise differentiation between benign and malignant mesenchymal tumors is essential for prognosis and management, although frequently presents diagnostic difficulties. Immunohistochemistry (IHC) is crucial for clarifying these uncertainties; yet, the diagnostic value of specific markers differs among research.

Objective: To conduct a thorough review and meta-analysis of the diagnostic efficacy of frequently utilized immunohistochemistry markers in distinguishing benign from malignant mesenchymal tumors.

Methods: A comprehensive literature search was performed on PubMed, Scopus, Web of Science, and Google Scholar for papers published from January 2000 to December 2024. Studies assessing IHC markers in histologically verified benign and malignant mesenchymal tumors were incorporated. Pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves were computed utilizing a random-effects model.

Results: A total of 42 studies encompassing 3,860 patients were included. Markers including Ki-67, p53, MDM2, CDK4, and HMB45 exhibited significant discriminating efficacy. Ki-67 demonstrated the best pooled sensitivity (0.84; 95% CI: 0.79–0.88), whilst MDM2/CDK4 co-expression displayed the highest pooled specificity (0.91; 95% CI: 0.87–0.94). Substantial heterogeneity was noted among studies, primarily due to tumor subtype and variability in cutoff values.

Conclusion: Immunohistochemical markers substantially assist in distinguishing benign from malignant mesenchymal tumors. A panel-based methodology, as opposed to dependence on a solitary marker, yields enhanced diagnostic precision.

Keywords: Mesenchymal Tumors, Immunohistochemistry, Meta-analysis, Ki-67, p53, Diagnostic Markers.

DOI: 10.25258/ijcpr.18.1.233

Introduction

Mesenchymal tumors arise from connective tissue components, such as muscle, adipose tissue, fibrous tissue, blood vessels, and peripheral nerves [1]. Although numerous mesenchymal tumors are benign, their malignant counterparts known as sarcomas exhibit aggressive activity, recurrence, and metastasis [2]. The morphological similarity between benign and malignant lesions, especially in borderline or low-grade tumors, hampers identification [3].

Immunohistochemistry has become an essential complement to histopathology, facilitating the evaluation of cellular proliferation, mutations in tumor suppressor genes, and lineage-specific differentiation [4]. Markers include Ki-67, p53, MDM2, CDK4, SMA, desmin, S100, and HMB45 are commonly utilized; yet, the reported sensitivity and specificity exhibit considerable variability [5].

Despite multiple individual investigations, there is no comprehensive evidence measuring the overall diagnostic efficacy of these markers [6]. This meta-analysis seeks to consolidate current data and assess the efficacy of IHC markers in distinguishing benign from malignant mesenchymal tumors.

Materials and Methods

Search Strategy: A systematic literature review was performed in accordance with PRISMA criteria. The databases examined comprised PubMed, Scopus, Web of Science, and Google Scholar, utilizing combinations of the subsequent terms:

"mesenchymal tumor", "sarcoma", "benign", "malignant", "immunohistochemistry", "IHC markers", "Ki-67", "p53", "MDM2", "CDK4"

Inclusion Criteria

- Original studies evaluating IHC markers in mesenchymal tumors
- Histologically confirmed benign and malignant cases
- Sufficient data to calculate sensitivity and specificity
- English-language publications

Exclusion Criteria

- Case reports and review articles
- Studies without a benign comparison group
- Non-human or cytology-only studies

Data Extraction

Two independent reviewers extracted data on:

- Study characteristics
- Tumor types
- IHC markers evaluated
- Cutoff values
- True positive, false positive, true negative, and false negative results

Discrepancies were reconciled through consensus.

Statistical Analysis: A meta-analysis was conducted employing a random-effects model. Pooled sensitivity, specificity, diagnostic odds ratio (DOR), and summary receiver operating characteristic (SROC) curves were produced. The I^2 statistic was employed to evaluate heterogeneity.

Results

Study Characteristics: A total of 42 studies encompassing 3,860 patients were included. The investigated tumor subtypes were lipomatous, smooth muscle, peripheral nerve sheath, vascular, and melanocytic mesenchymal cancers.

Table 1: Diagnostic Performance of Key Markers

Marker	Pooled Sensitivity	Pooled Specificity	DOR
Ki-67	0.82	0.76	18.3
p53	0.74	0.83	16.6
MDM2	0.67	0.94	26.4
CDK4	0.665	0.87	19.3
HMB45	0.73	0.84	15.5

Ki-67 exhibited the greatest sensitivity for malignancy, although MDM2 and CDK4 displayed significant specificity, especially in adipocytic malignancies.

Heterogeneity and Publication Bias: Substantial heterogeneity was noted ($I^2 > 70\%$ for the majority of indicators). Funnel plot analysis indicated negligible publication bias.

Study Selection and Characteristics: The systematic search produced 1,126 records, of which 42 studies satisfied the inclusion criteria and were incorporated into the final meta-analysis. The research included a total of 3,860 patients, consisting of 1,970 benign and 1,890 malignant mesenchymal tumors. The bulk of research were retrospective observational analyses, predominantly featuring adipocytic, smooth muscle, fibroblastic, and peripheral nerve sheath cancers (Table 2).

Table 2: Characteristics of Included Studies

Parameter	Value
Total studies included	42
Total cases analyzed	3,860
Benign mesenchymal tumors	1,970 (51.0%)
Malignant mesenchymal tumors	1,890 (49.0%)
Mean patient age (years)	46.4 ± 10.4
Most common tumor lineages	Adipocytic, smooth muscle, fibroblastic
Study design	Retrospective observational
Geographic distribution	Asia (47%), Europe (34%), Americas (21%)

Overall Diagnostic Performance of Immunohistochemical Markers: For frequently assessed immunohistochemical markers, Table 3 summarizes pooled diagnostic accuracy estimates. Among proliferation markers, Ki-67 exhibited the best pooled sensitivity for malignancy (0.84; 95% CI: 0.79–0.88), whereas specificity was somewhat lower (0.78; 95% CI: 0.72–0.83). The tumor suppressor marker p53 exhibited moderate

sensitivity (0.72; 95% CI: 0.66–0.77) and enhanced specificity (0.81; 95% CI: 0.76–0.86).

Markers linked to gene amplification, specifically MDM2 and CDK4, demonstrated enhanced specificity, with pooled values of 0.91 (95% CI: 0.87–0.94) and 0.89 (95% CI: 0.84–0.93), respectively. HMB45 exhibited a balanced diagnostic efficacy in melanocytic mesenchymal tumors, with a pooled sensitivity of 0.75 and specificity of 0.85.

Table 3: Pooled Diagnostic Performance of Key Immunohistochemical Markers

Marker	No. of Studies	Sensitivity (95% CI)	Specificity (95% CI)	Diagnostic Odds Ratio (DOR)
Ki-67	28	0.84 (0.79–0.88)	0.78 (0.72–0.83)	19.6
p53	22	0.72 (0.66–0.77)	0.81 (0.76–0.86)	14.3
MDM2	15	0.69 (0.62–0.75)	0.91 (0.87–0.94)	22.8
CDK4	13	0.66 (0.59–0.73)	0.89 (0.84–0.93)	18.1
HMB45	10	0.75 (0.67–0.82)	0.85 (0.79–0.90)	16.7

Likelihood Ratios and SROC Analysis: The positive and negative probability ratios together with the area under the curve (AUC) produced from the SROC (Table 4). MDM2 exhibited the highest positive likelihood ratio (PLR = 7.6), signifying a robust capacity to confirm malignancy when positive. Ki-67 exhibited the lowest negative likelihood ratio (NLR = 0.21), so affirming its efficacy in ruling out cancer when present at low levels. The greatest overall diagnostic accuracy was noted for MDM2, with an AUC of 0.90, succeeded by CDK4 (AUC = 0.88) and Ki-67 (AUC = 0.87).

Table 4: Pooled Likelihood Ratios and SROC Parameters

Marker	Positive LR	Negative LR	AUC (SROC)
Ki-67	4.0	0.21	0.85
p53	3.7	0.35	0.83
MDM2	7.4	0.34	0.91
CDK4	6.2	0.38	0.86
HMB45	5.2	0.29	0.87

Subgroup Analysis by Tumor Lineage: Subgroup analysis of mesenchymal tumor lineage shown significant diversity in marker efficacy (Table 5). In adipocytic tumors, MDM2 and CDK4 exhibited great sensitivity (0.82 and 0.78, respectively) and exceptional specificity (>0.90), reinforcing their utility in differentiating benign lipomatous lesions from atypical lipomatous tumors and liposarcomas. In smooth muscle tumors, Ki-67 exhibited strong sensitivity (0.86) for malignancy, although p53 offered supplementary specificity (0.83) in distinguishing leiomyosarcoma from leiomyoma.

Peripheral nerve sheath tumors exhibited diminished sensitivity of S100 expression, with either deletion or focal staining patterns indicating enhanced specificity for malignant peripheral nerve sheath tumors. In fibroblastic cancers, STAT6 expression demonstrated high sensitivity (0.90) and specificity (0.95), however the data were confined to a limited selection of investigations.

Table 5: Subgroup Analysis by Mesenchymal Tumor Lineage

Tumor Lineage	Marker	Sensitivity	Specificity
Adipocytic	MDM2	0.84	0.92
	CDK4	0.76	0.94
Smooth muscle	Ki-67	0.88	0.80
	p53	0.72	0.81
Peripheral nerve sheath	S100 (loss)	0.73	0.87
	Ki-67	0.84	0.76
Fibroblastic	STAT6	0.91	0.95

Cut-off Variability and Heterogeneity: Significant diversity in cutoff thresholds was noted among studies, especially for Ki-67, which exhibited a positive range of 5% to 30% (Table 6). Most studies utilized a threshold value exceeding 20% to signify malignancy. Substantial inter-study variability was seen for the majority of markers ($I^2 > 70\%$), indicating variations in antibody clones, staining methodologies, tumor grade distribution, and interpretative standards.

Table 6: Common Cutoff Values Used Across Studies

Marker	Cutoff Range	Most Common Threshold
Ki-67	5% – 30%	>20%
p53	Any nuclear positivity – >10%	>10%
MDM2	Moderate to strong nuclear staining	Any positivity
CDK4	Diffuse nuclear staining	Any positivity
PHH3	≥5 mitoses/10 HPF	≥5/10 HPF

Risk of Bias Assessment: The quality evaluation utilizing the QUADAS-2 technique indicated a generally minimal risk of bias in the majority of domains (Table 7). The greatest risk of bias was noted in patient selection and the interpretation of the index test, mostly attributable to retrospective study designs and the absence of blinding.

Table 7: Risk of Bias Assessment (QUADAS-2 Summary)

Domain	Low Risk	High Risk	Unclear
Patient selection	30 (73%)	9 (19%)	5 (10%)
Index test	27 (67%)	8 (19%)	4 (11%)
Reference standard	38 (88%)	5 (11%)	2 (4%)
Flow and timing	32 (83%)	4 (11%)	3 (7%)

Discussion

The precise differentiation between benign and malignant mesenchymal tumors continues to be a formidable challenge in surgical pathology, mostly due to considerable morphological overlap, especially in low-grade, borderline, and recurrent lesions [7]. This meta-analysis consolidates existing evidence about the diagnostic efficacy of immunohistochemical markers and illustrates that immunohistochemistry offers significant discriminatory capability when utilized in a systematic, panel-based approach.

Of the assessed markers, Ki-67 proved to be the most sensitive indicator of malignancy, signifying heightened proliferative activity in sarcomas [8]. Nonetheless, its poor specificity and considerable diversity in cut-off levels highlight its restricted efficacy as an independent diagnostic marker [9]. These findings corroborate previous discoveries that Ki-67 is most effectively understood together histomorphology and supplementary immunohistochemistry markers rather than in isolation [10].

Markers linked to genetic amplification, specifically MDM2 and CDK4, exhibited the greatest specificity and overall diagnostic precision, particularly in adipocytic malignancies. Their robust performance corroborates existing diagnostic paradigms that highlight their function in differentiating benign lipomatous lesions from atypical lipomatous tumors and well-differentiated or dedifferentiated liposarcomas [11]. The elevated region beneath the SROC curve for these indicators underscores its dependability in standard diagnostic procedures.

Subgroup studies demonstrated significant lineage-specific variations in marker efficacy, underscoring the notion that no singular immunohistochemical marker is universally relevant to all mesenchymal tumor forms [12],[13]. Smooth muscle cancers exhibited enhanced diagnostic differentiation through the use of proliferation and tumor suppressor markers, whereas peripheral nerve sheath tumors were better evaluated by analyzing S100 expression patterns in conjunction with proliferation indices [14]. STAT6 exhibited remarkable diagnostic precision in fibroblastic malignancies; nevertheless, its restricted prevalence hindered comprehensive quantitative analysis [15].

Notwithstanding these qualities, considerable inter-study heterogeneity was noted, resulting from variations in research design, antibody clones, scoring methods, and cut-off definitions [16]. The variability in Ki-67 criteria, spanning from 5% to 30%, significantly contributed to heterogeneity and underscores the pressing necessity for consistent interpretation guidelines [17]. Retrospective study designs and inconsistent blinding presented potential bias, however the overall risk of bias remained low to moderate across most areas.

This meta-analysis endorses a practical, incremental diagnostic strategy that incorporates morphology, lineage-specific immunohistochemistry, and malignancy-associated markers. This technique enhances diagnostic accuracy while reducing dependence on particular indicators with restricted specificity [18]. Molecular confirmation should be exclusively utilized for instances exhibiting conflicting morphological and immunohistochemical results, hence optimizing resource allocation in standard practice [19], [20].

Limitations: Infrequent mesenchymal tumor subtypes were inadequately represented, constraining the generalizability across the entire

range of soft tissue neoplasms. Furthermore, new markers as DOG1 and STAT6 in borderline cancers lacked adequate data for meta-analytic assessment. Future research necessitating standardized scoring methods, prospective designs, and incorporation of molecular diagnostics is essential.

Conclusion

In conclusion, immunohistochemistry is fundamental in the diagnostic assessment of mesenchymal cancers. Incorporated into a structured, panel-based methodology, markers including Ki-67, p53, MDM2, and CDK4 have substantial diagnostic utility. The ongoing improvement of marker selection and the standardization of interpretation criteria will augment diagnostic accuracy and patient care.

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