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Expression of P53 and KI-67 in Benign, Premalignant and Malignant Lesions of Gallbladder: A Comprehensive Review

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KEYWORDS

gallbladder carcinoma; p53; Ki-67; dysplasia; metaplasia–dysplasia–carcinoma sequence; proliferation marker; immunohistochemistry

ABSTRACT:

Gallbladder carcinoma (GBC) is an aggressive malignancy that often develops in the context of chronic inflammation, advancing through a sequence of metaplasia, dysplasia, and carcinoma. Differentiating reactive epithelial alterations from genuine premalignant lesions continues to pose a diagnostic challenge, underscoring the necessity for dependable molecular biomarkers.

Objective:

The goal of this review is to put together all the information we have about how the tumor suppressor protein p53 and the cellular proliferation marker Ki-67 are expressed in benign, premalignant, and malignant gallbladder lesions, and to see how useful they are for diagnosis and prognosis.

Methods:

A systematic review of peer-reviewed literature was performed, encompassing studies that evaluated p53 and Ki-67 expression in inflammatory, metaplastic, dysplastic, and malignant gallbladder lesions through immunohistochemistry. We looked at data about expression patterns, labeling indices, and how useful they were for diagnosis.

Results:

Benign and inflammatory gallbladder lesions consistently exhibited low Ki-67 labeling indices and wild-type p53 expression. Metaplastic changes and low-grade dysplasia exhibited slight elevations in Ki-67 and sporadic p53 positivity, indicating preliminary molecular modifications. In contrast, high-grade dysplasia and invasive gallbladder carcinoma displayed significantly elevated Ki-67 indices and robust, diffuse p53 expression, indicating heightened proliferative activity and genomic instability. These trends stayed the same, even though the cutoff values were different in different studies.

Conclusion:

The combined evaluation of p53 and Ki-67 improves the distinction among reactive atypia, premalignant lesions, and gallbladder carcinoma. Their expression is related to how aggressive a tumor is and how it changes into a malignant form, which supports their use as useful additional biomarkers for better diagnosis and early detection, especially in people at high risk.

Introduction

Gallbladder carcinoma (GBC) is a rare but extremely aggressive cancer that varies greatly by region and is disproportionately common in parts of East Asia, South America, and Northern India [1–3]. Chronic inflammatory injury is a major factor in causing epithelial instability and starting molecular changes that encourage neoplastic transformation. It is frequently linked to gallstones and chronic cholecystitis [2]. The most widely recognized pathogenetic model of

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gallbladder carcinogenesis over the past few decades is the metaplasia–dysplasia–carcinoma sequence [1,3,4]. However, it is still difficult to diagnose reactive atypia, metaplastic change, and true premalignant lesions based on histology, particularly in mucosa that is inflamed or architecturally distorted. Accurate recognition of lesions along this continuum is crucial because GBC frequently remains clinically silent until advanced stages, leading to poor prognosis and limited therapeutic options[1]. In this context, objective biomarkers indicative of proliferative activity and inherent genetic instability have become increasingly vital as supplementary instruments for risk stratification. Among these, p53, a tumor-suppressor protein whose aberrant nuclear accumulation typically indicates TP53 mutation, and Ki67, a proliferation-associated nuclear antigen that marks actively cycling cells, are the most extensively studied indicators of molecular progression[5-10].

Published literature consistently demonstrates a stepwise rise in both p53 overexpression and Ki-67 labeling index from benign and inflammatory lesions to metaplasia, dysplasia and ultimately invasive carcinoma[5-10]. Their combined evaluation has shown potential in improving diagnostic confidence, distinguishing reactive atypia from true dysplastic lesions, and correlating with tumor aggressiveness[7-10]. Nonetheless, discrepancies in staining patterns, interpretative criteria, and cutoff thresholds among studies require a comprehensive evaluation of the current evidence.

This review combines all the information we have about the expression of p53 and Ki-67 in benign, premalignant, and malignant gallbladder lesions. The goal is to make their diagnostic importance clearer, show how they work together, and give a full picture of how they help gallbladder tumors grow.

Materials and Methods

A systematic literature-search approach was used to find published data assessing the expression patterns and diagnostic value of p53 and Ki-67 in benign, premalignant, and malignant gallbladder lesions. The databases PubMed, Scopus, Web of Science, and Google Scholar were thoroughly searched electronically. Since the first significant immunohistochemical studies on gallbladder carcinogenesis were published in the early 1990s, articles published between 1990 and 2024 were taken into consideration. Gallbladder carcinoma, gallbladder dysplasia, p53 immunohistochemistry, Ki-67 labeling index, premalignant gallbladder lesions, metaplasia–dysplasia–carcinoma sequence, and proliferation markers were among the keywords and Boolean operators that were used, and they were combined using AND/OR.

Studies were included if they met the following criteria:

1. Original research articles published in peer-reviewed journals.

2. Studies assessing p53 and/or Ki-67 expression in gallbladder mucosa, encompassing chronic cholecystitis, metaplasia, dysplasia, and carcinoma.

3. Studies of human tissue using immunohistochemistry.

4. Articles providing quantitative or descriptive data on marker expression patterns.

5. Publications that are available in English.

The exclusion criteria were:

1. Letters, case reports, review papers, and conference abstracts.

2. Studies without clear immunohistochemical methodology or lacking numerical/qualitative data.

3. Articles evaluating only molecular genetics without immunostaining results.

4. Animal experiments or non-gallbladder lesions.

5. Datasets that are the same or overlap.

After a relevance screening of all titles and abstracts, the full texts of the studies that met the eligibility requirements were evaluated. Reference lists of key articles were manually searched to identify additional relevant publications, including classic foundational studies widely cited in gallbladder pathology literature. Data extracted from each selected study included sample size, histological categories assessed, immunohistochemical techniques, staining patterns, cutoff values, and trends in expression across the benign-to-malignant spectrum. Because of variability in scoring systems and thresholds among studies, a

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qualitative synthesis approach was used rather than meta-analysis.

There were no human subjects or patient-identifiable data involved in this review, so there was no need for ethical approval. It was assumed that all of the studies included followed the ethical standards set by their institutions, as stated by the authors.

Results and Discussion

The literature reviewed demonstrates a clear and progressive alteration in the expression profiles of p53 and Ki-67 across benign, premalignant and malignant gallbladder lesions. Epidemiological research indicates that chronic inflammation, especially in areas with elevated rates of gallbladder carcinoma, is a crucial factor in inducing epithelial damage and molecular instability [1-4]. Long-term cholelithiasis causes repeated damage to the mucosa, which leads to the progression from metaplasia to dysplasia and finally to carcinoma.

Findings consistently indicate that benign lesions, including chronic cholecystitis, show minimal proliferative activity and predominantly wild-type p53 expression, representing physiological epithelial regeneration[6,9]. Ki-67 labeling indices in these lesions typically remain <5–10%. Nonetheless, research indicates that chronically inflamed or contracted gallbladders may display marginally increased Ki-67 levels, indicating early biological stress without definitive neoplastic transformation [11].

In metaplastic epithelium and low-grade dysplasia, the expression of biomarkers starts to change. There is often a small but clear rise in Ki-67 that goes into the middle epithelial layers, along with p53 positivity that is patchy or focal[5,9]. These patterns show early molecular disarray caused by long-term inflammation, but they don't always mean that something is cancerous. The important change happens when these changes lead to high-grade dysplasia, which is when studies show a big jump in both biomarkers. Ki-67 values typically surpass 20–30%, with staining frequently nearing full-thickness involvement, whereas p53 exhibits pronounced and diffuse nuclear accumulation—serving as an immunohistochemical surrogate for TP53 mutation[7,8]. These results underscore the significance of p53 mutation and proliferative expansion in delineating authentic premalignant lesions.

In invasive gallbladder carcinoma, the expression of both markers rises significantly. Numerous studies indicate Ki-67 labeling indices surpassing 40–80%, especially in poorly differentiated tumors, signifying significant proliferative dysregulation [10,12,13]. Likewise, diffuse p53 positivity is commonly noted and has been linked to aggressive tumor behavior, lymphovascular invasion, advanced stage, and poor differentiation[8,14]. These trends underscore the importance of TP53 dysfunction as a critical molecular event in gallbladder carcinogenesis.

A consistent conclusion in the reviewed literature is that the simultaneous evaluation of p53 and Ki-67 offers enhanced diagnostic efficacy compared to each marker individually. Ki-67 is an early sign of proliferative expansion, and p53 overexpression shows that genomic damage has built up over time. Reactive atypia may show a small increase in Ki-67, but it usually doesn't have mutant-type p53 expression, which helps tell it apart from low-grade dysplasia. In high-grade dysplasia and carcinoma, there is a significant simultaneous increase in both markers, establishing a dependable immunohistochemical signature of neoplastic progression[5,7,10]. This dual-marker strategy is especially beneficial in areas where gallbladder cancer is prevalent and histological analysis may be difficult due to inflammation.

Despite general trends, there are differences between studies in cutoff values, staining intensity, and interpretation criteria. The reported Ki-67 thresholds range from 20% to 30%, and p53 scoring methodologies vary between percentage-based and qualitative mutant-type classifications. These methodological disparities highlight the necessity for standardized immunohistochemical protocols. Still, the evidence as a whole strongly supports the importance of p53 and Ki-67 in diagnosing, predicting, and understanding the biology of gallbladder tumors.

Conclusion

The cumulative evidence from published studies indicates a distinct, incremental progression in the expression of p53 and Ki-67 across benign, premalignant, and malignant gallbladder lesions. Benign and inflammatory mucosal changes generally demonstrate low proliferative activity and wild-type

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p53 expression, while metaplasia and low-grade dysplasia present with subtle yet significant elevations in both markers, indicating early molecular disruption caused by chronic inflammation. High-grade dysplasia and invasive carcinoma are marked by a sharp rise in Ki-67 labeling indices and strong, diffuse p53 positivity. This shows how important these biomarkers are for finding lesions that could become cancerous. Results from several studies demonstrate that the concurrent evaluation of p53 and Ki-67 enhances the differentiation between reactive atypia, dysplasia, and carcinoma, offers significant insights into tumor biology, and correlates with aggressive pathological characteristics. Even though different studies use different ways to score and different cutoff values, the overall trends stay the same. Adding these markers to diagnostic tests could make them more accurate, help grade premalignant lesions, and help find gallbladder cancer early, especially in areas where it is common.

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Ethical Statement

There are no experiments involving humans or animals in this review article; it is entirely based on previously published research. Because of this, there was no need for ethical approval or informed consent.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this review article.

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