Section: Pathology

Original Research Article

IMMUNOHISTOCHEMICAL EXPRESSION OF MUC-1 & MUC5AC IN GALL BLADDER DISEASES

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ABSTRACT

Background: Gallbladder cancer (GBC) is the most common malignancy of the biliary tract, arising from the epithelial lining of the gallbladder and cystic duct. It may present as diffuse wall thickening or as a mass lesion involving the fundus, body, or neck of the gallbladder. According to GLOBOCAN data, GBC accounts for approximately 1.2% of all cancer cases and 1.7% of cancer-related deaths worldwide. India is a high-incidence region, contributing nearly 10% of the global GBC burden. This study aimed to evaluate the immunohistochemical expression and clinicopathological significance of MUC1 and MUC5AC in gallbladder diseases. **Materials and Methods:** This prospective study was conducted in the Department of Pathology in collaboration with the Department of Surgery, GSVM Medical College, Kanpur. A total of 88 histologically confirmed cases of benign, premalignant, and malignant gallbladder lesions were included. Immunohistochemical staining for MUC1 and MUC5AC was performed, and their expression patterns were correlated with clinicopathological parameters. **Result:** Most patients belonged to the 51–70 years age group and were female. MUC1 expression increased progressively from benign to malignant lesions. Among benign cases, 74% showed low expression, while 26% demonstrated weak positivity. Premalignant lesions exhibited moderate expression in 56% of cases. Malignant lesions showed high MUC1 expression in 87.5% of cases, with strong staining in 81.2%. In contrast, MUC5AC expression was highest in benign lesions (81.4%), decreased in premalignant lesions (65%), and was markedly reduced in malignancies (25%). **Conclusion:** Progressive MUC1 overexpression and loss of MUC5AC are associated with gallbladder carcinogenesis. Their inverse expression pattern may serve as a useful indicator of malignant transformation, tumor aggressiveness, and disease progression in gallbladder lesions.

INTRODUCTION

Gallbladder cancer (GBC) is a highly aggressive malignancy arising from the epithelial lining of the gallbladder and cystic duct. It is the most common cancer of the biliary tract and is characterized by late clinical presentation, rapid progression, and poor prognosis. The disease may present as diffuse thickening of the gallbladder wall or as a mass involving the fundus, body, or neck of the gallbladder. According to GLOBOCAN data, gallbladder cancer accounts for approximately 1.2% of all global cancer diagnoses and 1.7% of cancer-related deaths worldwide, reflecting its high mortality rate despite relatively low incidence.[1] India represents a high-incidence region and contributes nearly 10% of the global burden of gallbladder cancer. The highest incidence rates are reported from North, North-East, Central, and Eastern India, suggesting the influence of regional environmental, dietary, infectious, and genetic factors in disease development.[2]

Gallstone disease (cholelithiasis) is one of the most important risk factors associated with gallbladder carcinoma. Approximately 80% of Indian patients diagnosed with gallbladder cancer have coexisting gallstones.[3] Chronic irritation of the gallbladder mucosa by gallstones induces persistent inflammation, epithelial injury, and regenerative changes, which may progress through metaplasia and dysplasia to invasive carcinoma. However, the disproportionately high incidence of gallbladder

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cancer in certain geographical regions indicates that additional factors such as chronic bacterial infections, environmental pollutants, dietary habits, and genetic susceptibility also contribute significantly to carcinogenesis.[4,5]

Mucins are high-molecular-weight glycoproteins synthesized and secreted by epithelial cells. They play a vital role in maintaining epithelial integrity by providing lubrication, hydration, and protection against mechanical, chemical, and microbial injury.[6,7] Mucins are encoded by a family of MUC genes and are broadly classified into secreted and membrane-bound types. Altered expression and glycosylation of mucins have been implicated in the pathogenesis of several inflammatory and neoplastic disorders, including gallbladder diseases.[8,9]

Among the various mucins, MUC1 and MUC5AC have attracted considerable attention because of their involvement in gallbladder carcinogenesis. MUC1 is a membrane-bound glycoprotein encoded on chromosome 1q21. Under normal physiological conditions, it functions as a protective barrier and contributes to epithelial homeostasis. However, in malignant tissues, MUC1 is frequently overexpressed and aberrantly glycosylated, promoting tumor cell proliferation, invasion, metastasis, and resistance to apoptosis. Increased MUC1 expression has been reported in several epithelial malignancies and is associated with poor prognosis and aggressive biological behavior.[10–13]

MUC5AC is a secreted gel-forming mucin predominantly expressed in epithelial tissues of the respiratory and gastrointestinal tracts. In the gallbladder, MUC5AC contributes to mucus production and mucosal protection. Overexpression of MUC5AC has been associated with increased mucus viscosity, bile stasis, cholesterol crystallization, and gallstone formation.[14,15] In contrast to MUC1, studies have suggested that MUC5AC expression tends to decrease during malignant transformation, indicating a possible protective role in the early stages of gallbladder disease.[16]

The differential expression patterns of MUC1 and MUC5AC during the progression from benign inflammatory lesions to premalignant and malignant gallbladder lesions suggest their potential utility as diagnostic and prognostic biomarkers. Understanding their expression profiles may provide valuable insights into the molecular mechanisms underlying gallbladder carcinogenesis and help identify markers of disease progression and tumor aggressiveness.

Therefore, the present study was undertaken to evaluate the immunohistochemical expression of MUC1 and MUC5AC in benign, premalignant, and malignant gallbladder lesions and to determine their clinicopathological significance. The findings may contribute to improved understanding of gallbladder tumor biology and aid in the identification of potential biomarkers for early diagnosis, prognostication, and targeted therapeutic strategies in gallbladder diseases.

MATERIALS AND METHODS

This prospective study was conducted over a period of two years in the Department of Pathology in collaboration with the Postgraduate Department of Surgery at GSVM Medical College and LLR & Associated Hospitals, Kanpur, to evaluate the immunohistochemical expression of MUC1 and MUC5AC in gallbladder diseases. A total of 88 histologically confirmed cases of chronic cholecystitis, premalignant lesions, and gallbladder carcinoma were included, while metastatic gallbladder carcinoma and post-chemotherapy/radiotherapy cases were excluded. Gallbladder tissue specimens obtained during surgical procedures were processed as 10% formalin-fixed, paraffin-embedded blocks, and 4-µm sections were subjected to immunohistochemical staining for MUC1 and MUC5AC. Expression was assessed according to the modified criteria of Jeon et al., with staining categorized as negative (<5% positive cells), low (<33%), moderate (33–66%), or high (>66%). Ethical approval was obtained from the Institutional Ethics Committee, and informed consent was secured from all participants. Data were entered into Microsoft Excel and analyzed using SPSS version 20. Associations between mucin expression and clinicopathological parameters were evaluated using the Chi-square test, with $p<0.05$ considered statistically significant, to determine the diagnostic and prognostic relevance of MUC1 and MUC5AC in gallbladder disease progression.

RESULTS

The study included 88 patients diagnosed with gallbladder diseases, comprising chronic cholecystitis, premalignant lesions, and gallbladder carcinoma. The demographic and clinical characteristics of these patients were analyzed in terms of age, gender, and clinical presentation.

Table 1: Age Distribution of Patients

Age Group (Years)	Number of Cases (n = 88)	Percentage (%)
18 – 30	5	5.7
31 – 50	25	28.4
51 – 70	55	62.5
>70	8	9.1
Total	88	100

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Most patients (62.5%, n=55) were aged 51–70 years, followed by 31–50 years (28.4%, n=25), while 9.1% (n=8) were over 70 years. The mean age of the study population was 56.8 ± 12.4 years [Table 1].

Table 2: Gender Distribution of Patients

Gender	Number of Cases (n = 88)	Percentage (%)
Male	22	25.0
Female	66	75.0
Total	88	100

A significant female predominance was observed in this study, as demonstrated in [Table 2]. Out of the 88 cases, 66 patients (75%) were female, while 22 patients (25%) were male. The female-to-male ratio was 3:1.

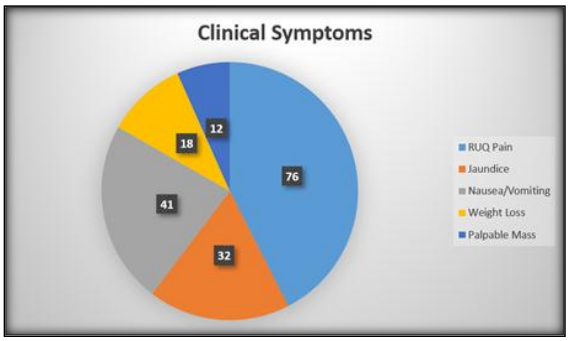

Figure 1: Pie chart for Clinical Symptoms and Presenting Complaints

Right upper quadrant pain was the most common symptom (86.3%, n=76), followed by nausea/vomiting (46.6%), jaundice (36.4%), weight loss (20.5%), and palpable abdominal mass (13.6%) [Figure 1].

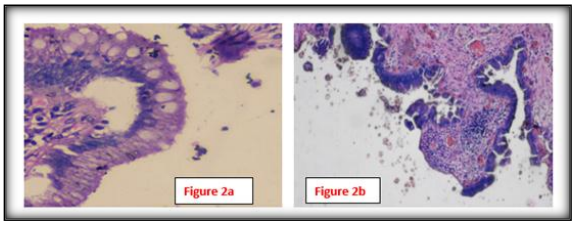

Figure 2: (2a) H&E stained slide showing intestinal metaplasia in gall bladder (X200). (2b) H & E stained slide showing dysplasia in gall (x200)

The histopathological diagnosis was categorized into benign (chronic cholecystitis), premalignant (dysplasia/metaplasia), and malignant (adenocarcinoma) lesions. The distribution of cases based on histopathological findings is summarized in [Figure 2].

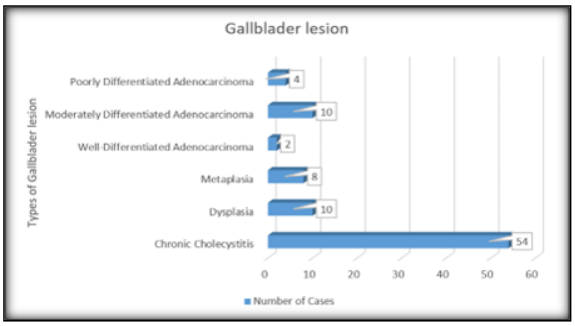

Figure 3: Bar chart for Histopathological Types of Gallbladder Lesions

Among the malignant cases, moderately differentiated adenocarcinoma was the most common subtype (62.5%), followed by poorly differentiated adenocarcinoma (25%), and well-differentiated adenocarcinoma (12.5%), as shown in (Figure 3).

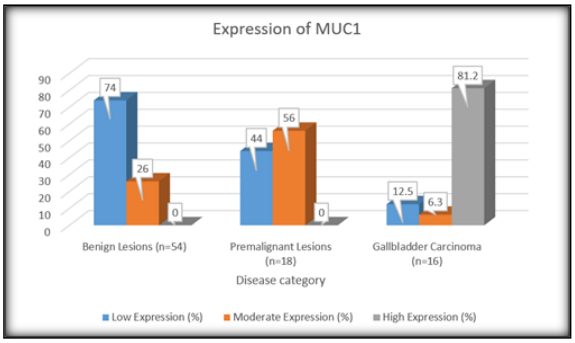

Figure 4: Bar chart for Expression of MUC1 in Benign, Premalignant, and Malignant Cases

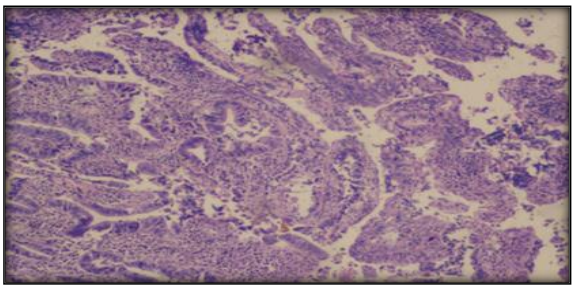

Figure 5: H & E stained slide showing well differentiated adenocarcinoma of gall bladder (x200)

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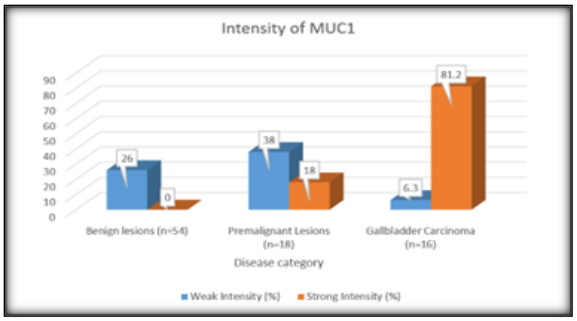

Figure 6: Bar chart for Intensity of MUC1 Expression in Various Lesions

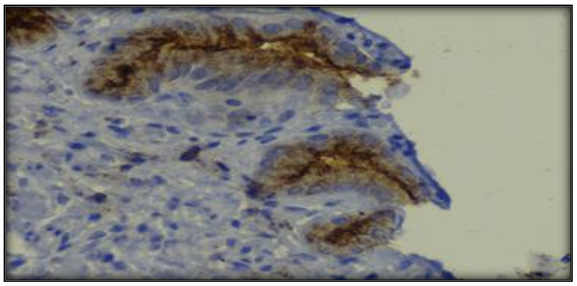

Figure 7: MUC 1 expression in gall bladder dysplasia is moderately high (x200)

Low MUC1 expression was observed in 74% of benign cases, while 56% of premalignant lesions showed moderate expression. In contrast, malignant lesions demonstrated high MUC1 expression in 87.5% of cases, with strong staining intensity in 81.2%, indicating a progressive increase from benign to malignant disease [Figure 4].

In the present study, MUC-1 expression in gall bladder diseases showing low expression in cholecystitis (x200) [Figure 5].

A significant association was observed between MUC1 intensity and malignancy ($p < 0.001$). Benign lesions mostly exhibited weak expression, whereas strong staining was predominant in carcinomas [Figure 6].

In the present study, MUC 1 expression in gall bladder dysplasia is moderately high (x200) [Figure 7].

Table 3: Correlation of MUC1 Expression with Tumor Grade

Tumor Grade	High MUC1 Expression (%)	Low/Negative Expression (%)
Well-Differentiated (n=2)	50	50
Moderately Differentiated (n=10)	80	20
Poorly Differentiated (n=4)	100	0

[Table 3] presents the correlation of MUC1 expression with tumor grade and staging. High-grade tumors demonstrated greater MUC1 positivity than well-differentiated tumors.

Table 4: Expression of MUC5AC in Benign, Premalignant, and Malignant Cases

Disease Category	Low Expression (%)	Moderate Expression (%)	High Expression (%)
Benign Lesions (n=54)	10	8.6	81.4
Premalignant Lesions (n=18)	20	65	15
Gallbladder Carcinoma (n=16)	75	0	25

The expression of MUC5AC varied significantly across gallbladder disease categories. [Table 4] summarizes the findings. MUC5AC was highly expressed in benign lesions (81.4%), while its expression declined in premalignant lesions (65%) and was markedly reduced in malignancy (25%).

Table 5: Intensity of MUC5AC Expression in Various Lesions

Disease Category	Weak Intensity (%)	Strong Intensity (%)
Benign Lesions (n=54)	22	78
Premalignant Lesions (n=18)	39	61
Gallbladder Carcinoma (n=16)	75	25

In the present study, MUC5AC staining intensity was evaluated as weak or strong. The results are provided in [Table 5].

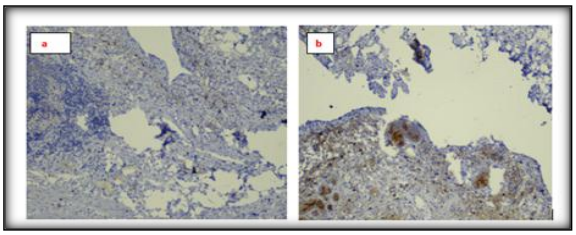

Figure 8: MUC-5AC expression in gall bladder diseases – 8a: MUC 5 AC expression is low in gall bladder carcinoma; 8b: MUC 5 AC expression is high in cholecystitis (x200)

MUC-5AC expression in gall bladder (x200) [Figure 8]

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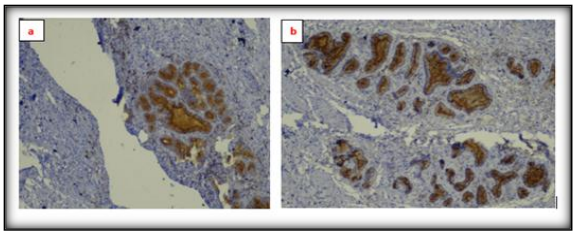

Figure 9 a & b: MUC 5AC is moderately high in metaplasia (x200)

In the present study, MUC 5AC is moderately high in metaplasia (x200) [Figure 9 a & b].

Table 6: Correlation of MUC5AC Expression with Tumor Grade

Tumor Grade	High MUC5AC Expression (%)	Low/Negative Expression (%)
Well-Differentiated (n=2)	60	40
Moderately Differentiated (n=10)	30	70
Poorly Differentiated (n=4)	0	100

[Table 6] illustrates that MUC5AC expression declined with increasing tumor grade.

Table 7: Comparative Analysis of MUC1 and MUC5AC Expression in Different Lesions

Disease Category	High MUC1 Expression (%)	High MUC5AC Expression (%)
Benign Lesions (n=54)	0	81.4
Premalignant Lesions (n=18)	0	65
Gallbladder Carcinoma (n=16)	87.5	25

The comparison of MUC1 and MUC5AC expression is presented in [Table 7].

Table 8: Statistical Significance of MUC1 vs. MUC5AC Expression in Gallbladder Cancer

Parameter	MUC1 Expression (p-value)	MUC5AC Expression (p-value)
Benign Lesions vs. Premalignant Lesions	0.04 (significant)	0.06 (not significant)
Benign Lesions vs. Gallbladder Carcinoma	< 0.001 (highly significant)	0.02 (significant)
Premalignant Lesions vs. Gallbladder Carcinoma	0.005 (significant)	0.03 (significant)

To determine the statistical significance of MUC1 and MUC5AC expression in gallbladder diseases, a comparative analysis was conducted, and the results are presented in [Table 8].

Table 9: Association of MUC1 Expression with Clinical Features

Clinical Feature	High MUC1 Expression (%)	p-value
Tumor Invasion	86.5	< 0.001
Lymph Node Metastasis	79.3	0.002

The relationship between MUC1 expression and clinical features is summarized in [Table 9]. High MUC1 expression was strongly associated with tumor aggressiveness, nodal metastasis, and poor prognosis.

Table 10: Association of MUC5AC Expression with Clinical Features

Clinical Feature	High MUC5AC Expression (%)	p-value
Tumor Invasion	18.2	0.04
Lymph Node Metastasis	22.5	0.03

The association between MUC5AC expression and clinical parameters is summarized in [Table 10].

Table 11: Chi-Square Analysis of MUC1 and MUC5AC Expression

Marker	χ^2 Value	p-value	Statistical Significance
MUC1	12.54	< 0.01	Highly Significant
MUC5AC	9.31	< 0.05	Significant

A chi-square analysis was conducted to determine the statistical association between MUC1 and MUC5AC expression in gallbladder disease progression. The results are summarized in [Table 11].

Table 12: P-Value Significance of MUC Expression in Gallbladder Diseases

Comparison	MUC1 Expression (p-value)	MUC5AC Expression (p-value)
Benign vs. Premalignant Lesions	0.04	0.06
Benign vs. Malignant Lesions	< 0.001	0.02
Premalignant vs. Malignant Lesions	0.005	0.03

The overall p-value analysis for MUC expression is presented in [Table 12].

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DISCUSSION

The present study was undertaken to evaluate the immunohistochemical expression of MUC1 and MUC5AC in various gallbladder diseases and to determine their clinicopathological significance. Gallbladder carcinoma remains one of the most aggressive malignancies of the biliary tract, often presenting at an advanced stage with poor prognosis. Therefore, the identification of reliable biomarkers capable of distinguishing benign, premalignant, and malignant lesions is of considerable clinical importance. In the present study, significant differences in the expression patterns of MUC1 and MUC5AC were observed among benign, premalignant, and malignant gallbladder lesions. The results demonstrated a progressive increase in MUC1 expression with disease progression, whereas MUC5AC expression showed a gradual decline from benign lesions to invasive carcinoma. These findings suggest that both mucins play important but contrasting roles in gallbladder carcinogenesis and may serve as useful biomarkers in assessing disease progression.

The analysis of MUC1 expression revealed a clear association between increased MUC1 expression and malignant transformation. Benign lesions predominantly exhibited low or weak MUC1 expression, whereas premalignant lesions showed moderate positivity and malignant lesions demonstrated strong expression in the majority of cases. These observations are consistent with previous studies that have highlighted the role of MUC1 in gallbladder cancer progression and aggressiveness.[19] MUC1 is a membrane-bound glycoprotein normally expressed on the apical surface of epithelial cells where it functions as a protective barrier. During malignant transformation, however, MUC1 undergoes overexpression and aberrant glycosylation, resulting in altered cellular adhesion, enhanced signaling activity, and increased metastatic potential.[21] Such molecular alterations contribute significantly to tumor progression and facilitate invasion into adjacent tissues.

The role of MUC1 in carcinogenesis has been extensively studied in several epithelial malignancies. Aberrant expression of MUC1 activates multiple intracellular signaling pathways involved in cell proliferation, survival, and migration. The cytoplasmic tail of MUC1 interacts with β-catenin, PI3K/Akt, MAPK, and NF-κB signaling pathways, all of which are known to promote tumor growth and inhibit apoptosis.[18] These signaling mechanisms enable malignant cells to evade normal growth control and acquire invasive characteristics. The findings of the present study support these molecular observations, as high MUC1 expression was predominantly observed in advanced-stage tumors and poorly differentiated carcinomas. This suggests that MUC1 expression not only reflects malignant transformation but also correlates with increasing biological aggressiveness.[21]

An important observation in the current study was the significant association between MUC1 expression and metastatic behavior. Cases exhibiting strong MUC1 positivity showed a greater tendency for lymph node involvement and distant spread. These findings are in agreement with earlier studies demonstrating that MUC1 overexpression contributes to tumor invasion and metastasis through modulation of cell adhesion molecules and activation of oncogenic pathways.[19] MUC1 has also been shown to interact with growth factor receptors such as EGFR and FGFR, resulting in enhanced cellular proliferation and migration. Such interactions facilitate tumor dissemination and contribute to poor clinical outcomes. Similar conclusions were reported by Benson et al., who observed a strong relationship between MUC1 expression and reduced survival in patients with biliary tract malignancies.[17]

The relationship between MUC1 expression and tumor differentiation observed in this study further emphasizes its prognostic significance. Poorly differentiated adenocarcinomas demonstrated the highest levels of MUC1 expression, whereas well-differentiated tumors exhibited comparatively lower expression. This finding suggests that increasing MUC1 expression accompanies loss of cellular differentiation and acquisition of a more aggressive phenotype. Previous investigations have similarly reported that MUC1 expression increases with higher histological grade and advanced disease stage, making it a valuable marker of poor prognosis.[19] Therefore, assessment of MUC1 expression may assist pathologists and clinicians in predicting tumor behavior and identifying patients at higher risk for disease progression.

In contrast to MUC1, MUC5AC expression showed a distinctly different pattern. High levels of MUC5AC expression were observed in chronic cholecystitis and premalignant lesions, whereas a marked reduction was noted in gallbladder carcinoma. These findings are consistent with reports by Khandeparkar et al. and Benson et al., who demonstrated that MUC5AC is highly expressed in normal and inflamed gallbladder epithelium but progressively decreases during malignant transformation.[17] MUC5AC is a secreted gel-forming mucin that contributes to epithelial protection by maintaining mucus viscosity and creating a barrier against mechanical and microbial injury. Its expression in benign lesions may therefore represent a protective physiological response to chronic inflammation and epithelial damage.[19]

The elevated expression of MUC5AC in chronic cholecystitis observed in this study may also be related to its role in gallstone formation. Previous studies have demonstrated that MUC5AC contributes to cholesterol crystal nucleation and gallstone development by increasing mucus

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viscosity and promoting bile stasis. Chronic inflammatory stimuli further enhance mucin secretion, resulting in increased expression of MUC5AC within the gallbladder epithelium. Vilkin et al. reported that excessive MUC5AC production creates a favorable environment for cholesterol crystal aggregation and gallstone formation, thereby contributing to the pathogenesis of chronic gallbladder disease. The present findings support this concept, as MUC5AC expression was highest among benign inflammatory lesions and declined progressively with disease advancement.

The reduction of MUC5AC expression in malignant lesions is particularly noteworthy. Several molecular mechanisms have been proposed to explain this phenomenon, including promoter hypermethylation, transcriptional repression, and alterations in mucin gene regulation during carcinogenesis.[21] As neoplastic transformation progresses, epithelial cells lose their normal secretory characteristics and acquire invasive properties. Consequently, the expression of protective mucins such as MUC5AC decreases. Kumar et al. suggested that loss of MUC5AC expression is associated with epithelial-mesenchymal transition (EMT), a process that promotes cellular migration, invasion, and metastasis [20]. The findings of the present study are consistent with this hypothesis, as reduced MUC5AC expression was associated with increased tumor invasion and lymph node metastasis. These observations indicate that loss of MUC5AC may serve as an early indicator of malignant transformation and disease progression.[20,21]

A particularly important finding of the study was the inverse relationship between MUC1 and MUC5AC expression. As MUC1 expression increased, MUC5AC expression decreased, suggesting that these mucins may play opposing roles in gallbladder carcinogenesis. MUC1 appears to function as a promoter of tumor progression, invasion, and metastasis, whereas MUC5AC seems to exert a protective effect during the early stages of disease. This reciprocal expression pattern has been reported in previous investigations and has been proposed as a molecular signature of malignant transformation.[19,22] The transition from a MUC5AC-dominant phenotype to a MUC1-dominant phenotype may therefore represent a critical event in the progression of gallbladder lesions from benign inflammatory conditions to invasive carcinoma.[19,22]

The clinical implications of these findings are substantial. Accurate differentiation between benign, premalignant, and malignant gallbladder lesions remains a diagnostic challenge, particularly in small biopsy specimens and early-stage disease. The distinct expression patterns of MUC1 and MUC5AC observed in this study suggest that these markers may provide valuable diagnostic information. Strong MUC1 expression combined with reduced MUC5AC expression may support a diagnosis of malignancy, whereas preservation of MUC5AC expression with minimal MUC1 positivity may favor a benign or premalignant lesion. The combined assessment of these mucins could therefore improve diagnostic accuracy and assist in histopathological interpretation. In addition to their diagnostic utility, MUC1 and MUC5AC may also serve as prognostic biomarkers. The strong association between MUC1 overexpression and aggressive clinicopathological features suggests that MUC1 assessment may help identify patients at increased risk of recurrence, metastasis, and poor survival. Similarly, loss of MUC5AC expression may indicate a higher likelihood of invasive behavior and adverse outcomes. Incorporation of these biomarkers into routine pathological evaluation could facilitate risk stratification and guide clinical decision-making.[22]

Recent advances in cancer therapeutics have further increased interest in mucin-targeted treatment strategies. MUC1 has emerged as a promising therapeutic target due to its frequent overexpression in several epithelial malignancies. Various MUC1-directed therapies, including monoclonal antibodies, cancer vaccines, immune checkpoint-based approaches, and small-molecule inhibitors, have shown encouraging results in preclinical and early clinical studies.[18] Given the significant overexpression of MUC1 observed in gallbladder carcinoma in the present study, future research should investigate the feasibility of MUC1-targeted therapies in patients with advanced gallbladder cancer. Such approaches may provide novel treatment options for a disease that currently carries a poor prognosis.[18]

Overall, the findings of the present study demonstrate that MUC1 and MUC5AC exhibit distinct and opposing expression patterns during gallbladder carcinogenesis. Progressive MUC1 overexpression is associated with malignant transformation, tumor aggressiveness, and metastatic potential, whereas MUC5AC expression is predominantly retained in benign and premalignant lesions and progressively lost during cancer progression. The inverse relationship between these two mucins highlights their importance in the pathogenesis of gallbladder disease and underscores their potential utility as diagnostic and prognostic biomarkers. These findings contribute to the growing body of evidence supporting the role of mucins in gallbladder pathology and provide a foundation for future studies exploring their clinical and therapeutic applications.

CONCLUSION

The present study highlights the significant diagnostic and prognostic value of MUC1 and MUC5AC expression in gallbladder diseases. MUC1 was found to be strongly associated with gallbladder carcinoma, tumor aggressiveness, and

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disease progression, whereas MUC5AC expression was predominantly observed in benign and premalignant lesions and progressively decreased with malignant transformation. The contrasting expression patterns of these mucins suggest their potential utility in differentiating benign, premalignant, and malignant gallbladder lesions. Combined evaluation of MUC1 and MUC5AC may improve diagnostic accuracy, facilitate risk stratification, and provide valuable prognostic information. Furthermore, these markers may serve as potential targets for future therapeutic interventions. Additional large-scale studies incorporating molecular analyses and long-term clinical follow-up are warranted to further validate their clinical significance and explore their role in targeted treatment approaches. Integration of MUC1 and MUC5AC assessment into routine pathological evaluation may contribute to earlier diagnosis, personalized management, and improved outcomes for patients with gallbladder diseases.

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