



## Original Research Article

## Histomorphological spectrum of gall bladder lesions, relation to p53 expression

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## ABSTRACT

**Introduction:** Gall bladder lesions include the varied spectrum of lesions encompassing inflammatory, benign, premalignant and malignant conditions. Progression from benign to malignant change is a complex process. The pathological importance of chronic inflammation leading to neoplasia has come into prominence in recent years. Multiple mechanisms are involved in the carcinogenesis and the most commonly disrupted gene is the p53 gene.

**Materials and Methods:** In our prospective study, of three consecutive years duration a total of 262 specimens which included inflammatory, premalignant, and malignant lesions of the gall bladder were received. Immunohistochemical analysis with a p53 antibody was done on selected 60 specimens according to our inclusion criteria.

**Results:** Of the received specimens majority (84.7%) were inflammatory lesions followed by precursor lesions (10.7%) and malignant lesions (4.5%). Chronic cholecystitis with cholelithiasis is the predominant lesion accounting for 33% of the cases. P53 expression was observed in 50% of malignancies and was not seen in any of the premalignant conditions. 11.8% of inflammatory lesions with thickened wall showed p53 expression.

**Conclusion:** The most common histopathological diagnosis was chronic cholecystitis. Chronic inflammation is a major risk factor for malignancy. Careful pathological examination of gallbladder specimens should be done as the neoplastic process may present silently as cholecystitis. P53 expression in chronic inflammatory conditions indicates an important role of inflammation in chronic cholecystitis-carcinoma sequence. Early detection of p53 mutation by Immunohistochemical analysis, and regular follow up aid in optimal patient management.

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## 1. Introduction

Gall bladder diseases present with diverse clinical and histopathological spectrum including congenital, inflammatory, benign, premalignant and malignant conditions.<sup>1</sup> The most common pathology occurring in the gallbladder is cholelithiasis followed by cholecystitis. Cholelithiasis is one of the common health problems encountered all over the world causing economic burden in the developing countries.<sup>2</sup> Very few studies have been done on the South Indian population and the frequency of the gallbladder

lesions especially in Telangana region, is not clear. There is a significant difference in the gall bladder diseases between North India and South India.<sup>3</sup> The incidence of gallbladder cancer in south India and its link to gallstone disease is not clearly established.<sup>3</sup>

Radiological diagnosis of gall bladder lesions may not be accurate at all times. Absolute diagnosis of the premalignant and malignant lesions is only possible on histopathologic examination of the specimen, as pre-operative imaging techniques fail to identify the lesions. Thus, it is important to study histopathological changes in order to determine the incidence, prevalence, and distribution of the lesions.<sup>4</sup>

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The progression from benign to malignant change is a multistep and age-dependent complex process.<sup>5</sup> Neoplasia arising from chronic inflammation has recently attracted increasing attention.<sup>6</sup> Studies done to observe the relation between chronic inflammatory conditions and carcinogenesis, have revealed that the most common mechanism is the disruption of the p53 gene which is called the "Guardian of the Genome." It is a tumor suppressor gene located on the Short arm of chromosome 17 which prevents potentially destructive mutations from building up in our DNA.<sup>7</sup> Many studies show that p53 has a role in the initiation and progression of carcinomas.<sup>8</sup>

P53 expression in chronic inflammatory lesions like chronic cholecystitis is significant in carcinogenesis.<sup>6,8</sup> Identification of malignant transformation in inflammatory and premalignant lesions might be a diagnostic challenge at times and identification of p53 mutation by immunohistochemistry (IHC) aids in diagnosis.

Gall bladder carcinoma (GBC) though very rare has poor prognosis and early diagnosis is essential for improving the quality of the patient's life.<sup>9</sup> It is important to identify high-risk groups for gallbladder cancer because of the dismal nature of this tumor.<sup>10</sup> Cholelithiasis is a well-established risk factor for gallbladder cancer. Various genetic alterations have been identified in the pathogenesis of GBC out of which the commonest is the mutation of p53 gene.<sup>9</sup> Recent studies have elaborated on the molecular mechanisms underlying the development of Gall bladder carcinoma (GBC) in the setting of chronic inflammation.<sup>6</sup> Persistent local inflammatory reactions may contribute to the initiation and progression of GBC by inducing genetic mutations leading to inactivation of tumor suppressor genes, inhibition of apoptosis, and activation of oncogenes.<sup>6</sup> After thorough review of the literature we have found that studies on p53 mutation have not been done on South Indian population. Though in our study we have used IHC to identify the mutation rather than molecular techniques, it is a cost effective and accurate technique which can be used in government setups and also where majority of the patients are poor.

The study of p53 mutation in gall bladder lesions by IHC may be useful for screening, early diagnosis of recurrence in the remaining biliary tract, spread to liver and follow up of at-risk patients.<sup>10</sup> Research on the gall bladder lesions and p53 mutation in Indian population is needed especially in South Indian region.

The present study was undertaken to

1. Identify the incidence of various lesions occurring in the gall bladder in our region.
2. Identify premalignant and malignant changes in chronic inflammatory lesions.
3. Determine the expression of the p53 nuclear protein on the selected sample lesions.
4. To identify the pattern of p53 mutation in Gall bladder carcinomas.
5. To compare the present study findings with other studies.

## 2. Materials and Methods

This prospective study was done in the department of pathology, at our institute for 3 consecutive years. We received 262 specimens which included congenital, inflammatory, premalignant, and malignant lesions of the gall bladder. The specimens were processed and stained routinely. IHC with p53 antibody using the Peroxidase – Anti peroxidase method has been done on 60 selected samples out of 262 specimens.

### 2.1. Inclusion criteria for performing IHC

All the premalignant and malignant conditions were selected for IHC. Chronic inflammatory lesions with thickened wall (>1cm) have also been included to examine their malignant potential. IHC analysis and microscopic examination for nuclear positivity was done, which was classified as diffuse, focal, and sporadic.

## 3. Results

A total of 262 specimens were received in 3 years with a variety of lesions including congenital, inflammatory, premalignant and malignant diseases (Table 1). In the present study, females outnumbered males with the male to female ratio of 1:1.2. The cases in our study belonged to different age groups. The youngest being 16 years and the oldest 70 years. Average age of occurrence in malignancies is 51.5 years.

Majority of the specimens received were inflammatory lesions (84.7%) followed by precursor lesions (10.7%) and malignant lesions (4.5%) (Chart 1). The inflammatory lesions comprised of chronic calculous cholecystitis (35.11%) Chronic cholecystitis (CC) (29.5%), CC with xanthogranulomatous change (9.92%), CC with gangrenous change (1.52%), CC with sinus histiocytosis (1.14%). We also had cases of acute cholecystitis (3.05%) and acute on chronic cholecystitis (4.58%). In the premalignant lesions, we had cystadenomas, choledochal cysts, polyps, CC with adenomyosis and CC with antral metaplasia. We also had one case of papillary serous cystadenoma (Table 1).

We had 12 malignant lesions in our study which included 6 cases of well-differentiated adenocarcinomas, four cases of moderately differentiated type and 2 cases poorly differentiated carcinoma. Well-differentiated adenocarcinomas included two cases of incidentally detected malignancies on cholecystectomy specimens. P53 expression was studied on selected 60 cases according to inclusion criteria (Table 2). The cases were observed for nuclear positivity. In our study the two cases which were

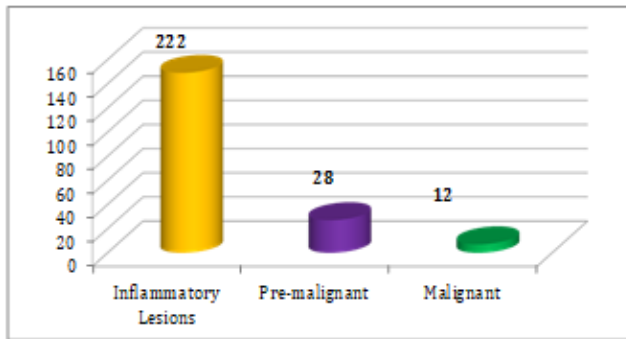


Chart 1: Broad spectrum of lesions received

**Table 1:** Various lesions encountered in our study

Lesions	Number of Cases	Percentage
Chronic Calculous Cholecystitis	92	35.11%
Chronic Cholecystitis With Adenomyosis	77	29.5%
With Xanthogranulomatous Reaction	09	3.43%
With Gastric Antral Metaplasia	26	9.92%
With Sinus Histiocytosis	05	1.90%
With Choledochal Cyst	03	1.14%
Gangrenous Cholecystitis	01	0.38%
Acute Cholecystitis	04	1.52%
Acute On Chronic Cholecystitis	08	3.05%
Biliary Cystadenomas	12	4.58%
Choledochal Cysts	02	0.76%
Polyps	08	3.05%
Papillary Serous Cystadenoma	02	0.76%
Malignancies	01	0.38%
Total	12	4.58%
	262	100%

detected incidentally had associated gallstones for which cholecystectomy was done. GBC was detected incidentally on histopathological examination. Other cases presented with right upper quadrant pain, jaundice, and a palpable mass

**Table 2:** Sample size for IHC study

S. No:	Lesion	No:	Total
1	Inflammatory	34	60
2	Pre malignant	14	
3	Malignant	12	

P53 expression was observed in 50% of malignancies which was seen in all the cases of poorly differentiated and moderately differentiated carcinomas (Figure 1). P53 expression was not seen in well-differentiated carcinomas and premalignant conditions. In the inflammatory lesions,

11.8% of chronic cholecystitis with thickened walls showed p53 expression (Figure 2, Table 3).

#### 4. Discussion

Cholecystitis and cholelithiasis are amongst the major causes of morbidity and mortality all over the world causing common health problems throughout developing countries. Cholecystectomy is one of the commonest surgical procedures and postoperative analysis of cholecystectomy specimen has great value since histopathological examination may reveal some lesions with significant clinical importance.<sup>1</sup>

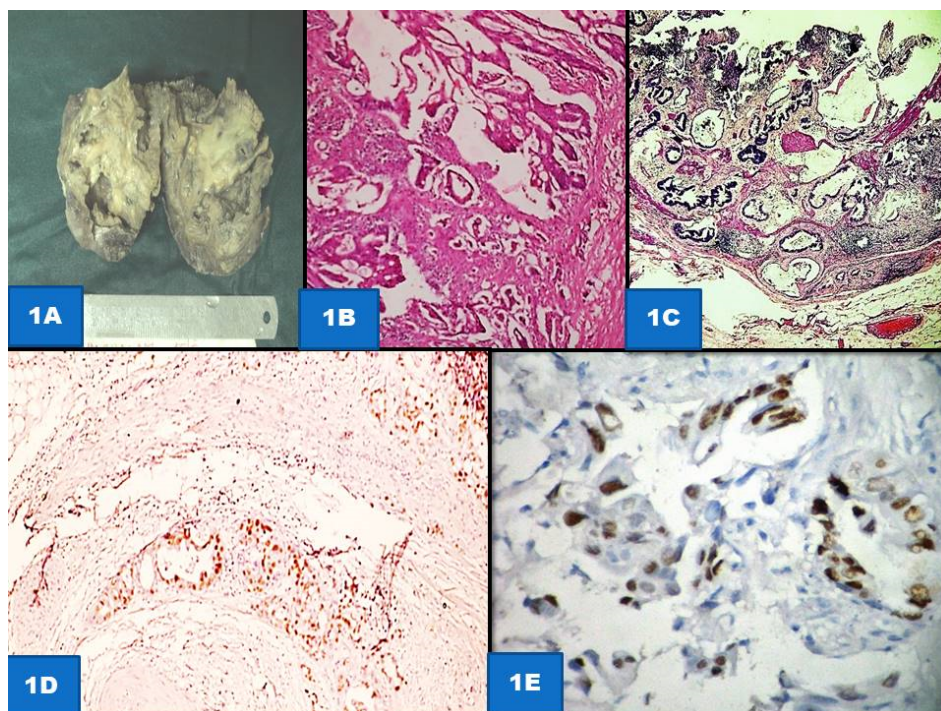
A wide spectrum of diseases ranging from congenital anomalies, non-inflammatory, inflammatory to the neoplastic lesions do affect the gallbladder.<sup>1</sup> Very few studies have been done on the South Indian population especially in Telangana region to know the incidence and prevalence of these lesions. There is a significant difference in the incidence and prevalence of diseases affecting the gall bladder in North India and South India.<sup>11</sup> Six Cancer registries of the Indian Council of Medical Research (1990–96) show a 10 times lower incidence of GBC per 100000 in South India compared with the North.<sup>12</sup> Gallbladder cancer is uncommon in south India and its association with gallstones is also low.<sup>3</sup>

In the present study, the age of the patients ranged from 18 years to 72 years and the average age at presentation was 46.3 years whereas in malignant lesions it was 51.5 years. The average age at presentation in various other studies is similar to our study.<sup>1,13</sup> It is well known that gall bladder diseases affect mostly women and frequently in middle age. Our study showed increased incidence of gall bladder lesions in females compared to males, many other studies reported the same.<sup>14–16</sup> Female sex hormones, especially estrogen, sedentary lifestyle, lead to gall stone formation.<sup>13,17</sup> A large number of studies have proposed that estrogen increases the risk of developing cholesterol gallstones by increasing the hepatic secretion of biliary cholesterol, which, in turn, leads to an increase in cholesterol saturation of bile leading to gallstones.<sup>17</sup>

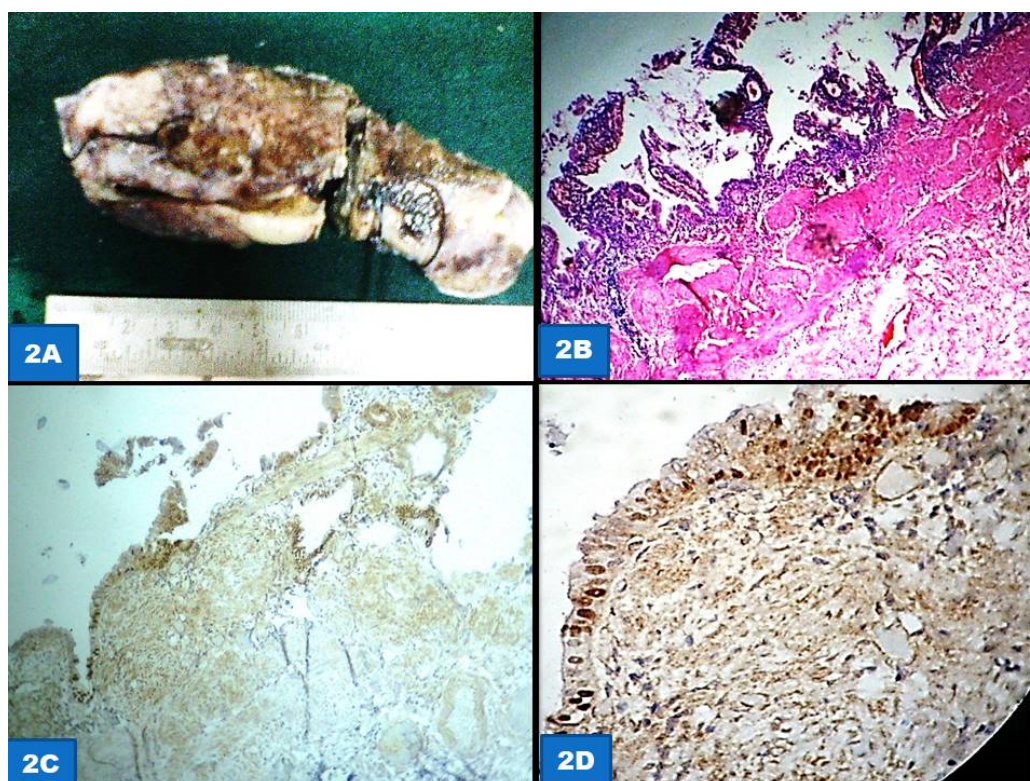
##### 4.1. Inflammatory lesions

In our study, inflammatory lesions constituted the majority (84.7%) followed by precursor lesions (10.7%) and malignant lesions (4.58%). Chronic cholecystitis is the commonest disease of the gall bladder and is the most important indication for cholecystectomy. Most cases of cholecystitis were associated with cholelithiasis which is a common disorder afflicting 10-20% of the adult population.<sup>13,16</sup> Repeated attacks of inflammation leads to fibrosis and thickened wall. In our study chronic cholecystitis was associated with other conditions like gall stones, adenomyosis, metaplasia, xanthogranulomatous





**Fig. 1:** A): Gross specimen of Gallbladder carcinoma; B): Moderately differentiated adenocarcinoma, H&E low power view; C): Incidentally detected case of well differentiated carcinoma on cholecystectomy specimen, H&E scanner view; D): p53 nuclear positivity in a case of moderately differentiated adenocarcinoma, H&E low power view; E): p53 nuclear positivity in the same case H&E high power view



**Fig. 2:** A): Gross specimen of chronic cholecystitis with thickened wall; B): Microscopic picture of chronic cholecystitis, H & E scanner view; C): p53 nuclear staining in a case of chronic cholecystitis, scanner view; D): p53 nuclear staining in the same case high power view

**Table 3:** Pattern of P53 expression

Type of Lesion	No of Cases	P53 Positive Cases	P53 Negative Cases	Percentage of Positive Cases
Inflammatory	34	04	30	11.8%
Pre Malignant	14	00	14	00%
Malignancies	12	06	06	50%

reactions, etc. Similar findings were observed in many national and international studies.<sup>9,11,13,14,16</sup>

Risk factors for cholecystitis include female sex, increasing age, pregnancy, oral contraceptives, obesity, diabetes mellitus, ethnicity.<sup>14,16</sup> CC occurs after repeated episodes of acute cholecystitis and is almost always due to gallstones.<sup>18</sup> In our study also we encountered cases of acute cholecystitis and acute on chronic cholecystitis.

#### 4.2. Premalignant lesions

Gall bladder polyps larger than 1.5cm are associated with a 50% risk of malignancy.<sup>19</sup> Choledochal cysts are also associated with a high risk of malignant transformation. Patients with these lesions may develop gallbladder carcinoma at a much younger age even in the absence of inflammatory risk factors like gall stones.<sup>20</sup> Premalignant lesions like cystadenomas, polyps, choledochal cysts were encountered in our study. Similar findings were observed by Shukla et al, Renuka et al, Thamil et al, and others.<sup>9,13,14</sup>

#### 4.3. Gall bladder carcinoma

Gallbladder carcinoma, though rare, is the most common malignancy of the biliary tract.<sup>1</sup> It is the 5<sup>th</sup> most common gastrointestinal malignancy accounting for 80%–95% of biliary tract cancers.<sup>10,21</sup> An early diagnosis is essential as GBC progresses silently with a late diagnosis, often proving fatal. Its carcinogenesis follows a progression through metaplasia–dysplasia–carcinoma sequence.<sup>21</sup> GBC is characterized by rapid progression with a high mortality rate. Cancers at an early stage are limited to the mucosa.<sup>22</sup> The lack of a serosal layer of gallbladder adjacent to the liver, enabling hepatic invasion and metastatic progression is one of the major causes of its miserable prognosis.<sup>21,22</sup>

There is an alarming trend in the incidence of gall bladder cancer in India.<sup>23</sup> Mohandas et al from Tata Memorial hospital, Mumbai, India, found that many patients with GBC were women with substantial family responsibilities. A large majority of them were diagnosed to have advanced GBC, suitable only for palliation.<sup>24</sup> In our study also all the cases of malignancies were female patients in their 5<sup>th</sup> decade. Mohandas et al, concluded that a strong correlation existed between long standing gall stone disease and gall bladder cancer. They also suggested that prophylactic cholecystectomy should be offered to young healthy women from high-risk regions of India whenever

they are diagnosed to have asymptomatic gallstones.<sup>24</sup> Population-based observational studies have to be started to find out the exact prevalence of this disease in Telangana region.

In some cases, GBC is incidentally detected in cholecystectomy specimens.<sup>21,22</sup> Vague presenting symptoms often delay the diagnosis of gallbladder cancer, contributing to its overall progression and poor outcome. Elderly age, female sex, congenital biliary tract anomalies, and a genetic predisposition represent important risk factors.<sup>21,22</sup>

GBC is preceded by gallstones, chronic cholecystitis and dysplastic changes of the gallbladder epithelium. The knowledge of the molecular events involved in its pathogenesis is scarce.<sup>25</sup> In recent times chronic gallbladder inflammation has been implicated as a major risk factor for malignant transformation.<sup>26</sup> Surgery represents the only potential for cure. Early diagnosis is very rare, and made only in incidentally detected cases. Late presentation implies advanced staging, nodal involvement, and possible recurrence following attempted resection. Overall mean survival is just 6 months, while the 5-year survival rate is only 5%.<sup>10,21,22</sup>

In our study we have focused on the incidence of gall bladder carcinoma in Telangana region of South India.

We had 12 (4.6%) cases of malignancies comprising of well-differentiated adenocarcinoma, moderately differentiated type and poorly differentiated carcinomas. In our study, we encountered 2 cases where malignancy was detected incidentally on cholecystectomy specimens done for cholecystitis. (Figure 1)

All the cases of malignancies were detected in females between 50 to 60 years age group. Our results correlate with the findings of Terada et al,<sup>2</sup> Aarti et al,<sup>21</sup> Hundal et al<sup>22</sup> and other researchers.<sup>1,9–11</sup> An early diagnosis is essential for proper management & better prognosis GBC progresses silently with a late diagnosis, often proving fatal.<sup>9,21,22</sup>

#### 4.4. Inflammation and carcinogenesis

The main risk factor for GBC is gallstone disease (GSD), which leads to a constant inflammatory state stimulated by recurrent cycles of cell death and regeneration of the epithelial layer. Patients with gallstone disease have a 21 to 57 fold increase in the risk of developing GBC.<sup>27</sup> Persistent local inflammatory reactions may contribute to the development and progression of GBC by inducing genetic alterations like inactivation of tumor suppressor genes, inhibition of apoptosis and promoting cell

survival.<sup>4,8,13,27</sup> Many recent studies have indicated a close relationship between chronic inflammation and neoplasia.<sup>28</sup> Recurrent or persistent inflammation may induce, promote, or influence susceptibility to carcinogenesis by causing DNA damage, inciting tissue reparative proliferation, and/or creating a stromal "soil" that is enriched with cytokines and growth factors.<sup>29</sup> The p53 gene encoded on chromosome 17p is an important regulator of cellular proliferation and its mutational inactivation facilitates carcinogenesis and malignant progression.<sup>6,7</sup> The P53 tumor suppressor gene has been studied in most types of cancer, its impact on the pathogenesis of GBC remains obscure.<sup>29,30</sup> Some studies have concluded that P53 abnormalities are early and frequent events in the pathogenesis of GBC, starting from chronic cholecystitis.<sup>27</sup> Inflammation may promote early alteration of P53, possibly through increased cell turnover and oxidative stress, although the precise mechanisms are unknown. Inactivation of the TP53 gene, either by deletion or mutation, is the most common genetic alteration observed in GBC, and as the frequency of TP53 alterations increases there is impairment of epithelial architecture and progresses from metaplasia to invasive carcinoma occurs.<sup>27</sup>

There is scarce information about the role of p53 mutation in GBC especially in Telangana region. Our study was also aimed to observe the p53 protein expression in various gall bladder lesions and to observe any malignant change in premalignant and chronic inflammatory lesions. Few studies, noted the expression of p53 in dysplasia's and carcinomas of the gall bladder suggesting that p53 mutation may be a common genetic alteration in the pathogenesis of GBC.<sup>25,26</sup> Understanding the molecular events in gallbladder carcinogenesis may provide a novel targeted therapeutic approach. The role of p53 gene in the pathogenesis of GBC can be determined by using IHC techniques on inflammatory, premalignant lesions and early carcinomas.<sup>31</sup>

P53 expression was seen in 50% of the malignant lesions in our study. (Figure 1C, D, E) Roa I et al also from their study observed that p53 expression was seen in up to 50% of the advanced carcinomas compared to early carcinomas.<sup>31</sup> Yasuhiro Oohashi et al, from their study, reported that p53 protein overexpression occurs as an early event in carcinogenesis and this alteration is maintained during its progression,<sup>32</sup> but this was in contradiction to our study findings where we did not observe any p53 expression in early/well-differentiated adenocarcinomas but strong p53 expression was seen in poorly differentiated and moderately differentiated carcinomas. Our findings are similar to the observations by Soon Lee et al,<sup>33</sup> Amitha et al,<sup>34</sup> M Teh et al.<sup>28</sup>

Soon Lee et al, in their study found p53 expression only in poorly differentiated adenocarcinoma and was associated with poor survival.<sup>33</sup> Amitha chaube et, al observed p53 overexpression with the increasing grade of

GBC and suggested its role in tumor progression rather than initiation.<sup>34</sup> M Tech et al, observed from their study that 50% of advanced carcinomas showed p53 positive expression compared to early carcinomas which were similar to our study findings.<sup>28</sup>

Shen-Nien Wang et al,<sup>35</sup> suggested that aberrant p53 expression may play a role in the occurrence of GBC. Ignacio et al<sup>36</sup> observed a progressively increasing incidence of p53 overexpression from premalignant lesions to invasive carcinomas, which is in contradiction to our study where premalignant lesions did not show any p53 clinically important amounts of p53. Similar findings were observed by Ajki et al in their study where p53 expression was negative in premalignant conditions.<sup>37</sup>

The over-expression of P53 protein in gallbladder carcinoma is a biomarker correlating with a poor survival. Some studies have showed that cases with over-expression of P53 on the peritumor epithelium, had early recurrence developed at the biliary tract. The immunohistochemical staining of the gallbladder wall or surgical stump for a surgical specimen of GBC may be crucial to predict the bile duct recurrence.<sup>38</sup> Immunostaining for P53 expression is necessary to predict the carcinogenesis of the remnant bile duct.<sup>38</sup>

Recent studies have emphasized the role of chronic inflammation in the pathogenesis of GBC. The main risk factors are prolonged exposure to gallstones, bacterial infections and other inflammatory conditions. The recurrent episodes of gallbladder epithelial damage and repair enable a chronic inflammatory environment that promotes progressive morphological alterations leading to metaplasia–dysplasia–carcinoma, along with cumulative genome instability.<sup>39</sup> P53 gene which is mutated in over 50% of GBC cases, seems to be the earliest and one of the most important carcinogenic pathways involved. Increased cell turnover and oxidative stress promote early alteration of p53, cell cycle deregulation, apoptosis and replicative senescence.<sup>25,39</sup> CC is the most important inflammatory lesion predisposing to the development of malignancy. In some studies, p53 is expressed in chronic inflammatory lesions like chronic cholecystitis.<sup>4,23,34</sup> In our study, 11.8% of the selected cases showed p53 expression in CC cases with thickened and inflamed gall bladder wall. (Figure 2: A, B, C, D) Similar findings were observed in other studies by Yasuhiro Oohashi et al,<sup>32</sup> where p53 expression was seen in 8.6% of the inflammatory conditions. In a study by Kenichi Kanoha et al, 14.3% of inflammatory lesions showed p53 expression.<sup>38</sup> They concluded that chronic cholecystitis with thick and sclerotic wall caused by recurrent inflammation could be an early change leading to carcinogenesis.

Yanagisawa et al,<sup>27</sup> concluded that sporadic p53 transition mutations were demonstrated in non-neoplastic lesions such as severe cholecystitis indicating the importance for chronic cholecystitis – carcinoma sequence in gall

**Table 4:** Comparison with other studies with other studies

Study by	No: of lesions		P53 expression
Shen- Nien Wang et al	Carcinomas	22	Carcinomas 13 (59.1%)
	Precursor lesions	17	Precursors 03 (17.6%)
	Inflammatory lesions	13	None
Yaasuhiro Oohashi et al	Carcinomas	41	Carcinomas 24 (58.5%)
	Inflammatory	23	Inflammatory 02 (8.6%)
Soon Lee, Anne Pirdas et al	Carcinomas	13	Carcinomas 09 (69.23%)
	Inflammatory	11	Inflammatory 01 (09%)
Kenichi Kanoha et al	Inflammatory	28	Inflammatory 04 (14.3%)
Amita Chaube et al	Carcinomas	40	Carcinomas 08 (20%)
	Inflammatory	23	None
Present study	Carcinomas	12	Carcinomas 06 (50%)
	Pre malignant	14	Pre malignant 00 (00%)
	Inflammatory	34	Inflammatory 04 (11.8%)

bladder carcinogenesis. Tazuma S et al,<sup>40</sup> studied the impact of chronic inflammation and gall stones in gall bladder carcinogenesis. They proposed that at molecular level chronic inflammation of the gall bladder and may lead to loss of p53 heterozygosity and excessive expression of p53 protein. Kanoh and Shimura et al<sup>38</sup> also showed the significance of chronic contracted cholecystitis with thickened and sclerotic wall as a risk factor for carcinogenesis (Table 4).

## 5. Conclusion

Gall bladder diseases have a wide spectrum of presentation histopathologically. Inflammatory lesions constituted the majority (84.7%) followed by precursor lesions (10.7%) and then malignant lesions (4.5%). In this study, the most common histopathological diagnosis was chronic cholecystitis. The incidence of gall bladder carcinomas in our region is less compared to North India. P53 expression was observed in 50% of malignancies which included moderately differentiated and poorly differentiated carcinomas and correlates with increasing tumor grade. In the inflammatory lesions, 11.8% of cases showed p53 expression. P53 gene mutation which is the commonest genetic alteration occurring in GBC can be accurately detected with conventional immunohistochemical techniques and aid in early identification of malignant transformation in inflammatory and premalignant lesions. Understanding the molecular events in gallbladder carcinogenesis may provide a novel targeted therapeutic approach. Long standing gallstones and chronic cholecystitis are risk factors for the development of GBC and careful pathological examination of all gallbladder specimens should be done as malignancy can be an incidental finding. Detection of p53 mutation in the gallbladder wall or surgical stump helps in predicting the recurrence or carcinogenesis of the remaining biliary tract. Early detection of p53 mutation using IHC can be taken up in Government set ups also as it is a cost effective method and aid in optimal care and management patient.

## 6. Source of Funding

None.

## 7. Conflict of Interest

None.

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