

# Study of gall bladder disease with incidence of gall bladder malignancy

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## Abstract

**Background:** To identify and evaluate the predisposing factor in gall bladder disease prospectively and to study the incidence of gall bladder malignancy in gall bladder disease. **Methods:** The present study included 240 patients who were distributed in three groups. About 198 patients of cholelithiasis, 27 patients of carcinoma gall bladder and 15 other patients of gall bladder disease were included. Findings of the patients were tabulated to reach the possible association of the factors concerned with a particular gall bladder disease. **Results:** The highest incidence of carcinoma gall bladder was in 7<sup>th</sup> decade of life in females and 6<sup>th</sup> decade in males and the highest incidence of cholelithiasis in 6<sup>th</sup> decade for males as well as females. Carcinoma gall bladder in females was 2.375 times more than males while this ratio in gallstones was 1: 2.54 in favor of females. **Conclusion:** Gallstone associated symptoms are non-specific and accurate diagnosis cannot be relied on clinical assessment alone. Careful clinical evaluation can guide patient selection for diagnostic imaging and appropriate management of those found to harbor stones.

**Keywords:** Cholelithiasis, Carcinoma gall bladder, Gall bladder disease

## Introduction

Gall bladder disease, although as old as history of medicine, still remains the world-wide problem and an enigma for modern medical science. Carcinoma of gall bladder is the commonest malignancy of biliary tract and the fifth most common gastrointestinal malignancy [1]. Despite advances in imaging techniques which permits early diagnosis, surgical techniques which allow more extensive procedures to be performed and post-operative care which reduced post-operative morbidity and mortality, carcinoma gall bladder remains a disease with dismal prognosis with overall survival rates of less than 10% at five years. Though the exact etiology of gall bladder malignancy remains unknown several well-known epidemiological characteristics provides avenues for further researches [2,3].

An extensive, although seemingly imperfect etiopathological bases of gall stones formation, their complications and treatment has been etched out. Gall bladder spectrum of disease extends far beyond these two entities and includes congenital anomalies and infective disease among other sufferings, the detailed

enumeration of which is beyond the need of description in this introduction [4]. Most of the studies in gall bladder disease especially carcinoma gall bladder have been retrospective. In this study we have tried to decipher and study the gall bladder disease (especially gall stones and carcinoma gall bladder), prospective to study the various factors that makes gall bladder disease the source of one of the major suffering in Central India [5].

## Materials and Methods

**Type of study:** Prospective

**Selection of the patients-** On admission or during examination in the OPDs, a detailed history and clinical examination was carried out, the requisite investigations like haemoglobin, total leucocyte count, differential leucocyte counts, serum bilirubin, alkaline phosphate, serum cholesterol level were done. Clinical diagnosis was made after this with help of specific investigations like ultrasonography and computerized tomography.

If required the patients underwent operative procedures after informed consent. None of the female patients who were pregnant were made part of the study.

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## Original Research Article

**Inclusion criteria:** Patients with history and diagnostic features suggestive of liver disease and its complication of age group 15 to 60 years of both male and female.

**Exclusion criteria:** Liver disease like alcoholic hepatitis, viral hepatitis other than liver disease. Patients who are not willing for specific investigations like USG, CT and aspiration of the abscess. The present study was carried out on patients by the author at various tertiary care centres either as OPD patients or as admitted patients in surgery department of various hospital.

The cases were divided into three groups-

**1. Carcinoma Gall Bladder:** Out of 240 patients, 27 cases were carcinoma gall bladder diagnosed on the basis of clinical profile, ultrasonography and computerized tomography.

**2. Cholelithiasis:** 198 out of 240 patients suffered from cholelithiasis, diagnosis was made with clinical examination and ultrasonography

**3. Others:** All the others were the patients in this some clinical, diagnostic or operative finding was noticed involving gall bladder.

**Methodology:** The methodology of the study work consists of filling up of the proforma constituted to cover all the important risk factors pertaining to gall bladder disease. With the filling of proforma it was tried to cover the important factors pertaining to the person itself and the factors included in the environment around the person. The person was followed during his clinical and biochemical pathological, radiological and if present the surgical management of the person. Even when the person went away from the hospital he was followed to track the investigation and the management the patient received. Findings of the patients were tabulated to reach the possible association of the factors concerned with a particular gall bladder disease.

**Statistical Analysis-** The data of the present study were fed into the computer and after its proper validation, checking for error, coding and decoding were compiled and analysed with the help of SPSS 11.5 software for windows. Appropriate univariate and bivariate analysis and ANOVA (analysis of variance) for more than two means were carried out using t-test and  $\chi^2$  test were calculated and tested. All means are expressed as mean + standard deviation. The critical values for the significance of the results were considered at 0.05 levels.

## Results

The highest incidence of carcinoma gall bladder was in 7th decade of life in females and 6th decade in males and the highest incidence of cholelithiasis is 6<sup>th</sup> decade for males as well as females. Carcinoma gall bladder in females was 2.375 times more than males while this ratio in gallstones was 1: 2.54 in favour of females. Mean duration of symptoms were 10.36 months in case of females and 9.89 months in case of males in case of cholelithiasis and 15.4 months in case of males and 16.5 months in case of females in carcinoma gall bladder. Most patients of carcinoma gall bladder presented with pain while most patients with cholelithiasis presented with flatulence, dyspepsia, distension of abdomen. There was a significant difference in level of bilirubin level in patients of carcinoma gall bladder and cholelithiasis when compared with each other. Conditions having more exposures of reproductive hormones predispose to gall bladder stones and weakly positively associated with carcinoma gallbladder (in case of females only). Mean cholesterol level in gallstone disease was more than 250 mg/dl while it was less than 250 mg/dl in case of carcinoma gall bladder disease.

**Table-1: Symptoms Noted in the Gall Bladder Disease**

Symptoms	Gallstones		Ca gall bladder		Others	
	No	%	No	%	No	%
Pain	120	60.6	25	92.59	4	26.66
Jaundice	10	5.05	8	29.62	2	13.33
Abdominal distension	126	63.53	2	7.4	4	26.66
Nausea	78	39.39	17	62.96	6	40
Vomiting	78	39.39	17	62.96	6	40
Anorexia	10	5.05	24	88.88	0	0
Decreased appetite	10	5.05	24	88.88	0	0
Weight loss	7	3.53	25	92.59	0	0
Malaise	34	17.17	21	77.77	4	26.66
Salty sweat	76	38.38	10	37.03	2	13.33

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Most patients of carcinoma gall bladder presented with pain while most patients with cholelithiasis presented with flautulance, dyspepsia, distension of abdomen.

**Table-2: Past/Ongoing Illness/ Significant Events.**

Symptoms	Gallstones		Ca gall bladder		Others	
	No	%	No	%	No	%
Hypertension	27	13.63	3	11.11	3	20
Diabetes	30	15.15	6	22.22	2	13.33
Previous jaundice episodes	10	5.05	9	33.33	2	13.33
Thyroid disease	21	10.60	2	7.4	1	6.66
Liver disease	2	1.01	8	29.62	2	13.33
Pregnancy history	136	68.68	19	70.37	2	13.33
History of any endocrinopathy	32	16.16	6	22.22	2	13.33

**Table-3: Reproductive History (Females Only).**

Exposures to hormones	No.	%	No.	%	No.	%
More exposure conditions	115	80.98	13	68.42	5	45.45
Less exposures conditions	27	19.01	6	31.57	6	54.54

Conditions having more exposures of reproductive hormones predispose to gall bladder stones and weakly positively associated with carcinoma gallbladder (in case of females only)

**Table4: Dietary History.**

Dietary habits	Cholelithiasis		Ca gall bladder	
	No	%	No	%
Vegetarian	100	50.50	14	51.85
Non vegetarian	98	49.49	13	48.14
Frequent sweet intake	97	48.98	10	37.03
Less or minimal diary product intake	130	65.65	19	70.37
Fruits intake	30	15.15	3	11.11
More oily food intake	87	43.93	14	51.85
More spicy food intake	97	48.98	13	48.14

**Table-5: Personal Habits**

Personal habits	Cholelithiasis		Ca gall bladder	
	No	%	No	%
Tobacco user	77	38.88	13	48.14
Non tobacco user	121	61.11	14	51.85
Alcoholic	50	25.25	10	37.03
Non alcoholic	148	74.74	17	62.96

**Table-6: Relation with alcoholism (Male Patients Only)**

Groups	Total patients	Alcoholic patients	%
Cholelithiasis	56	40	71.25%
Ca gallbladder	8	3	37.5%

## Discussion

A variety of risk factors have been proposed in the etiopathogenesis of carcinoma gallbladder but none has stood the test of time. Cholelithiasis had a strong association with gall bladder malignancy, chronic trauma and inflammation are considered to be the cause of this association, chronic cholecystitis, porcelain gall bladder, xanthogranulomatous cholecystitis, benign neoplasm and anatomical variation have also been correlated with carcinoma gallbladder. Several other risk factors like endogenous and exogenous chemical carcinogens / co –carcinogens have been implicated in gall bladder carcinogenesis, among them industrial pollutant methyl cholanthrene, O-amino azotoluene, nitrosoamine, carbon tetra chloride, free radicals, lipid peroxidation products and secondary bile acids are noted ones.

Layde PM, Vessey MP et al did a cohort study of young women attending family planning clinics in which they studied risk factors for gall-bladder disease. About seventeen thousand women aged 25-39 years were recruited to the Oxford/Family Planning Association Contraceptive Study. 227 of these women had suffered surgically confirmed gall-bladder disease during the follow-up period, an incidence of 1.47 per 1000 woman-years. Obesity was by far the strongest risk factor for gall-bladder disease, but late age at first term birth and cigarette smoking also had statistically significant independent effects. The influence of the use of oral contraceptives on risk was small [6].

Shaffer EA studied epidemiology of gallbladder stone disease. Certain risk factors for gallstones are immutable: female gender, increasing age and ethnicity/family (genetic traits). Others are modifiable: obesity, the metabolic syndrome, rapid weight loss, certain diseases (cirrhosis, Crohn's disease) and gallbladder stasis (from spinal cord injury or drugs like somatostatin). The only established dietary risk is a high caloric intake. Protective factors include diets containing fibres, vegetable protein, nuts, calcium, vitamin C, coffee and alcohol, plus physical activity [7].

Friedman GD, Kannel WB et al did longitudinal observations for ten years on 5209 men and women aged 30–62 in Framingham, Massachusetts. The overall incidence of gallbladder disease was about twice as high in women as in men, and it increased with age in both sexes without any evidence of an excess in the forties. Increase in weight and number of pregnancies were each associated with increased incidence. Despite the

presence of cholesterol in many gallstones and the elevation of serum cholesterol often noted with obesity and during pregnancy, no relationship was demonstrated between serum cholesterol level and gallbladder disease. Hemoglobin level was also not related in the population studied. Women with lower systolic blood pressures showed a somewhat reduced risk of gallbladder disease, but the possibility that a mutual relationship to weight could explain this has not been excluded. Potent environmental factors influencing the rate of development of gallbladder disease have yet to be identified. On the basis of present evidence, it would appear that more attention should be devoted to the anatomy and pathological physiology of the biliary tract in seeking a better understanding of the pathogenesis of gallbladder disease[8].

Stinton LM, Shaffer EA. Postulated that the best epidemiological screening method to accurately determine point prevalence of gallstone disease is ultrasonography. Many risk factors for cholesterol gallstone formation are not modifiable such as ethnic background, increasing age, female gender and family history or genetics. Conversely, the modifiable risks for cholesterol gallstones are obesity, rapid weight loss and a sedentary lifestyle. The rising epidemic of obesity and the metabolic syndrome predicts an escalation of cholesterol gallstone frequency. Risk factors for biliary sludge include pregnancy, drugs like ceftioxone, octreotide and thiazide diuretics, and total parenteral nutrition or fasting.

Diseases like cirrhosis, chronic hemolysis and ileal Crohn's disease are risk factors for black pigment stones. Gallstone disease in childhood, once considered rare, has become increasingly recognized with similar risk factors as those in adults, particularly obesity. Other than ethnicity and female gender, additional risk factors for gallbladder cancer include cholelithiasis, advancing age, chronic inflammatory conditions affecting the gallbladder, congenital biliary abnormalities, and diagnostic confusion over gallbladder polyps [9].

Henson DE, Albores et al in their study on carcinoma of the gallbladder in which they studied histologic types, stage of disease, grade, and survival rates, they inferred that grade, histologic type, stage of disease, and vascular invasion were correlated with outcome. Compared with all other histologic types of cancer, papillary carcinomas had the most favorable prognosis. The 2-year survival rate for patients with papillary

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carcinoma was 47%. A correlation with survival existed between grade, stage of disease, and vascular invasion. The study confirmed that cancers of the gallbladder occur more often in older age groups and are more common in women. Almost 40% of cases are found at an advanced stage. For patients whose enolase tumor was limited to the gallbladder at the time of surgery, the 2-year survival rate was 45% and the 5-year rate was 32% [10-13].

Sampliner RE, Bennett PH et al did their study on gallbladder disease in Pima Indians and demonstrated high prevalence and early onset by cholecystography. The overall prevalence of gallbladder disease was 48.6 per cent, which greatly exceeded that based on clinical diagnosis alone. The prevalence was significantly higher in females and increased with age in both sexes. No association was demonstrated between gallbladder disease and obesity, serum cholesterol level, diabetes or parity. Pima females 15 to 20 years of age were shown to be at high risk of early development of gallbladder disease and to offer unusual opportunities for further epidemiologic and clinical studies [14].

An interesting study relating abdominal symptoms and gallstone disease was done by Jørgensen T. To examine this issue, the relationship between occurrence of gallstone disease diagnosed by ultrasonography and complaints about abdominal pain and discomfort was assessed in a random sample. As regards the presence of gallstones, the predictive values of various complaints about pain and discomfort were very low, ranging from zero to 25.0%, whereas for the absence of gallstones the predictive value of no complaints about pain or discomfort was very high, ranging from 93.2 to 94.2%.

In subjects with gallstones, the prevalence of upper right quadrant pain during the last 12 months was equal to that in subjects with a normal gallbladder, whereas in chole-cystectomized subjects the prevalence of pain was significantly higher. Pain was not associated with size, number or motility of the stones. It is concluded that in a random population it is difficult to define the symptoms specific for gallstones and thereby to distinguish between symptomatic and asymptomatic gallstones. The mean duration of symptoms in our study was 10.56 months in case of females and 9.89 months in case of males, which corresponds with the presentation of most of the symptomatic gall stones patients within one year [15]. Portincasa P, Moschetta A et al studied symptoms and diagnosis of gallbladder stones. They also evaluated the clinical aspects and the diagnostic features of gallstone disease. The natural history of

silent gallstones is overviewed, and the risk of developing symptoms and complications is also discussed. The importance of colicky pain as a specific gallstone symptom is highlighted, and the role of both laboratory tests and diagnostic investigations for differential diagnosis is discussed. Finally, they described the diagnostic features of gallbladder stone disease, including indications, sensitivity, specificity, and limitations of different test investigations under special circumstances [16].

Diehl AK, Sugarek NJ did clinical evaluation for gallstone disease and studied usefulness of symptoms and signs in diagnosis. Patients with gallstones who have recently experienced biliary tract pain are likely to develop recurrent symptoms in the near future. As a consequence, most symptomatic patients are offered specific treatment. However, disagreement persists regarding which symptoms and signs truly represent symptomatic cholelithiasis. We re-examined the relation of gastrointestinal complaints and physical findings to the presence of gallstones in a clinical population.

Upper abdominal pain is the symptom most closely associated with gallstone disease. Radiation to the upper back, a steady quality, duration between 1 and 24 hours, and onset more than an hour after meals support the diagnosis [17].

**Conclusion**

Gallstone-associated symptoms are non-specific, and accurate diagnosis cannot rely on the clinical assessment alone. Careful clinical evaluation can guide patient selection for diagnostic imaging and the appropriate management of those found to harbor stones. To confirm the association of gallbladder disease with smoking, alcohol, diet, fat intake, fruits intake etc. and incidence of it converting into a carcinoma is difficult. To assess the exact incidence of malignancy; a case control study is required.

**Conflict of interest:** None declared.

**Funding:** Nil, **Permission from IRB:** Yes

**Ethical approval:** Taken

**What this study adds to existing knowledge:**

Gallstone-associated symptoms are non-specific, and accurate diagnosis cannot rely on the clinical assessment alone. Careful clinical evaluation can guide patient selection for diagnostic imaging and the appropriate management of those found to harbor stones. To diagnose it as carcinoma gall bladder is a difficult entity.

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