

# Gallbladder pathologies and cholelithiasis

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## ABSTRACT

**Objective:** Cholecystectomy, mostly due to cholelithiasis is one of the most common surgical procedures utilizing a significant amount of healthcare resources. As there are a huge number of cases, for example approximately 300 cases per year in our region, outlines this commonly encountered lesion should be recorded. Also, in an attempt to delineate the outline of the pattern, age and sex distribution of gallbladder diseases in the whole Kingdom, a comparative analysis is also included in this study with 7 other studies published from different parts of the Kingdom.

**Methods:** Our study consisted of 740 consecutive gallbladder cholecystectomies mostly for cholelithiasis received in a time frame of 3.5 years (for example between January 1997 through to May 2000) by the Department of Histopathology retrieved from the records of the laboratory. The outline of main gallbladder pathologies was tabulated. The number of gallbladders received with stones was also calculated. Age and sex distribution for gallbladder pathology and gallstones was also tabulated.

**Results:** There were 131 males (18%) and 609 (82%) females, with a female ratio male 4.6:1. Benign lesions comprised 99% (mean age 36), mostly chronic cholecystitis (97%) and acute cholecystitis which constituted 15 cases only (2%), malignant lesions comprised only 7 cases for example 1% of all lesions (mean age 65).

**Conclusion:** Gallbladder pathologies are very common and similar results have been obtained from other studies by comparative analysis. The mean cholecystectomy rates in the Kingdom totalled approximately 10%, mean age for all cholecystectomy diseases in both sexes equalled 37.05. The mean age for males was 42.26, females 37.25 and their ratio was 44.5:1.

**Keywords:** Gallbladder lesions, gallbladder malignancy, chronic cholecystitis, cholelithiasis, cholesterosis.

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Cholecystectomy is the most common surgical procedure and as described in literature approximately 600,000 cholecystectomies are performed each year in the United States of America (USA), and gallstone related disease accounts for an estimated overall cost of more than 5 billion dollars annually in USA. This shows the importance of this organ and requires the pathologist to be familiar with the normal anatomy, histologic characteristics and pathologic states of this organ.<sup>1</sup> While the advent of laparoscopic cholecystectomy has revolutionized the manner in which routine gallbladder surgery is performed, it has not altered the type of specimen that the pathologist receives for processing. With a few exceptions, the diagnosis of disorders of the

gallbladder is quite straight forward, as most diseases are associated with cholelithiasis. When they are encountered at the time of frozen section, they often presented with a great diagnostic challenge, even for pathologists with extensive experience. The mean rate of cholecystectomy with respect to total number of operations was 5%, which is not as high as reported by other studies from the Kingdom of Saudi Arabia approaching 15%.<sup>2-3</sup> The exact prevalence of gallbladder pathologies and gallstones is still unknown for the Kingdom of Saudi Arabia. The majority of the studies from the Kingdom of Saudi Arabia have entertained the surgical techniques and interventions especially the laproscopic procedures.<sup>4-12</sup> Reports from the

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Kingdom of Saudi Arabia have suggested that the problem is very common.<sup>2,3</sup> A very large study from 14 hospitals of the country's Eastern province had reported that the frequency of cholecystectomies has increased by 98%, a finding not explained by the 67% increase in the population or the 87% increase in other operation rates.<sup>11</sup> This led us to analyze 740 surgical cholecystectomy specimens received in the Department of Surgical Pathology, King Abdul University Hospital (KAUH), Jeddah, Kingdom of Saudi Arabia during the time frame of 3 years and 4 months (from January 1997 to May 2000).

**Methods.** King Abdul Aziz University Hospital is a 250 (functional) bedded tertiary care hospital located in Jeddah. In an attempt to delineate the spectrum of gallbladder lesions, data on these surgical specimens carried out between January 1997 and May 2000 was retrieved from the records of the laboratory, keeping track of age, sex, histopathological diagnosis and presence of stones. All gallbladder specimens are received in formalin since prompt fixation is required for the mucosa, which is quite susceptible to bile-related autolysis. A total of 3 full-thickness sections (one each from fundus, body, and neck/cystic duct region) of the gallbladder are routinely taken and placed in one or 2 cassettes. Pericyclic duct lymph node if present is also sampled. If gallstones are not readily apparent, the bile is strained to assess for minute stones or floating cholesterol polyps, and the viscosity of the bile is described in the gross description of the specimen. The detailed characteristic of the stones is also mentioned in the gross description. Most of the times the gallbladder is received open, with stones retrieved by the surgeons. In these cases the description provided by surgeons regarding stones on the request form are followed.

**Results.** We analyzed all the gallbladder specimens over a time period of 40 months, and found a total of 740 specimens. We came across a total of 740 cases. The mean age was 36. There were 609 (82%) females and 131 (18%) males with a female to male ratio of 4.6:1 with seven of the cases (1%) having carcinoma. Gallstones were found in 576 specimens (78%) and their distribution in each.

**Discussion.** It is a common impression that gallstones are remarkably "common" in Saudis;<sup>12</sup> no exact prevalence figures are available. Comparison of the prevalence of gallstones among different populations is notoriously difficult not only with differences in availability of diagnostic facilities and attitudes toward treatment, but many patients who have gallstones remain symptom free.<sup>13</sup> Thus, in Great Britain, only one in 7 individuals with gallstones results in cholecystectomy,<sup>14</sup> whereas in

**Table 1** - Overall diagnosis of all gallbladder specimens with percentage having stones.

Diagnosis	Frequency*	%	n (% having stones**)
Acute cholecystitis	16	2	455 (74)
Chronic cholecystitis	613	83	15 (94)
Acute suppurative cholecystitis	2	0	2 (100)
Chronic cholecystitis with cholesterosis	81	11.5	79 (97.5)
Porcelain gallbladder	4	0.5	4 (100)
Chronic cholecystitis with metaplasia	17	2)	15 (88)
Carcinoma	7	1	6 (86)
<b>Total</b>	<b>740</b>	<b>100</b>	<b>576 (78)</b>

\*Number of patients with each diagnosis, n=number  
 \*\*Percentage of patients in each diagnosis which had stones

one population-based Italian study, 78% of subjects found to have gallstones were asymptomatic.<sup>15</sup> Three major factors can be implicated in gallstone formation, increased biliary cholesterol, decreased bile acids and nucleation defect(s).<sup>16</sup> Certain subjects attributable risk-factors were thought to modulate these gallstone formation factors. Irreversible risk factors including age and sex, possible reversible factors include obesity, parity, oral contraceptives, family history of gallstones, smoking, diabetes mellitus, plasma lipids, dietary factors and possibly major abdominal surgery.<sup>17</sup> There are a lot of inconsistencies in the literature with regard to these factors. Although we have not specifically concentrated on risk factors of gallstone formation in the present study they are briefly discussed as of their importance in the subject. There is one study reported from Medina Munawara<sup>12</sup> in which these risk factors of gallstone formation in young women are discussed separately. In the present study we have concentrated more on gallbladder pathologies and have calculated the rates of stones in each diagnosis. It has been estimated that approximately 20 million people in the USA have gallstones and approximately half of them are asymptomatic. Gallstones are described to be present in almost all the cases of chronic cholecystitis.<sup>18-27</sup> In our study, gallstones were found in 78% of all specimens. They were found in

79% of female specimens with the peak age in the 3rd decade, and 71% of males with peak age in the 4th decade. This figure might not represent the true picture of prevalence of stones in cholecystectomy specimens as most of the time the stones are handed over by the surgeons to patient relatives as a grant. But we have tried to be as precise as possible by following the descriptions reported by surgeons on histopathology request forms. Cholelithiasis has been described as the most prevalent disorder of the biliary system.<sup>1,28-30</sup> At least 10% of the adult population of the USA harbor gallstones. In the pediatric age group gallstones are quite uncommon (0.13-0.22%). Stones grow for the first 2 to 3 years, after which their growth stabilizes.<sup>27</sup> In literature, ultrasound surveys have shown a female to male ratio of 2-3:1 in the younger adult age groups and an increasing female prevalence with age. After age 60, the prevalence of gallstones in men and women is 10% to 15% and 20% to 40%. Major risk factors include older age (peak, 6th and 7th decades), female sex, multiple pregnancies, obesity or rapid weight loss, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol (but not elevated serum cholesterol) and ethnic predisposition. There were 81 specimens with cholesterosis totalling 11%. In literature, cholesterosis is reported in approximately 20% of cholecystectomy specimens.<sup>27</sup> This is characterized by the accumulation of cholesterol esters and triglyceride in aggregates of subepithelial macrophages and, to a lesser extent, in the gallbladder epithelium itself.<sup>8,9,11</sup> Patients with this condition were mostly women such as 73 cases (12%) with a mean age of 34 years. It has been described that cholesterosis may clinically improve after cholecystectomy.<sup>31</sup> Although the origin of cholesterosis is unknown, most theories stress that either supersaturation of the bile with cholesterol, which is found in many but not all cases, or abnormal lipid transport across the mucosa leads to the formation of the lipid deposits. Bile cholesterol supersaturation is also seen with cholesterol gallstones.<sup>27</sup> In our study gallstones were found in only 45% of the specimens. Literature from the west shows that more than 50% of surgically resected gallbladders, but only 10% of autopsied gallbladders with cholesterosis have gallstones (usually cholesterol type), however, this demonstrates the inconsistent relationship between these 2 conditions. There is no association of cholesterosis with elevated blood cholesterol.<sup>22,27</sup> In most cases of cholesterosis, the gross macroscopic description showed yellow, nonpolypoid, punctuate deposits in a diffuse distribution. They look like the surface of a strawberry hence, the term strawberry gallbladder. Metaplastic epithelium in the gallbladder can be divided into 2 major groups, namely, gastric (pyloric gland and surface epithelial) and intestinal, although there is also a rare squamous variety.<sup>32-35</sup> The changes

increase in frequency with age, they are more numerous in the context of gallstones, can be quite focal, and can involve any region of the organ. In our series metaplastic epithelium was found only in 17 (3%) of cases of which 15 (83%) were associated with stones. These were then subclassified into subtypes, there as 15 (88%) pyloric and 2 (12%) with intestinal metaplasia. No squamous metaplasia was reported in our series. Reports from the west have shown that pyloric gland (pseudopyloric, antral, or mucous gland) metaplasia is most common and is found in 66%-84% of cholecystectomy specimens.<sup>27</sup> Lobules of meta-plastic pyloric glands are usually scattered in the lamina propria, although they may extend through the muscular layer. Small submucosal nodules or polyps may result, often associated with overlying papillary hyperplasia. They have often been reported in the literature as a form of hyperplastic polyp. Intestinal metaplasia represents replacement of the normal epithelium by cells with an intestinal phenotype (goblet cells, endocrine cells, Paneth cells, and absorptive cells, rarely with a distinct brush border) and has been reported in 12% to 52% of gallbladders removed for cholelithiasis or chronic cholecystitis.<sup>10-35,36-44</sup> Squamous metaplasia is rare (<0.1% of cholecystectomy specimens).<sup>11,45,46</sup> It may be associated with porcelain gallbladder or squamous dysplasia or be found adjacent to invasive squamous cell carcinoma. So the rate of metaplastic changes were very low in comparison with the west. This might be explained by the fact that some pathologist do not describe mild metaplastic changes in their reports and also as most metaplastic changes occur focally, a more thorough sampling and careful interpretation of changes is required to get the accurate rates. There were 16 cases of acute cholecystitis and 2 cases of acute suppurative cholecystitis making 11% of total together. All of them were found to be associated with gallstones. These studies were composed of a smaller number of patients, having a lower statistical power. Reports from the west have shown variable rates of acute cholecystitis in cholecystectomy cases, but overall 5%-10% is reported by the majority of reports.<sup>47</sup> There were only 7 cases of gallbladder carcinoma in our study. One of them occurred in a male and was diagnosed as an invasive papillary carcinoma, 6 in females as well, as moderately differentiated adenocarcinoma. The mean age for carcinoma was 65 years. There were 2 cases in females which occurred in the late 3rd decade but the rest of them occurred only in more than 75 age group. Amazingly reports from the west have shown carcinoma of the gallbladder as the most common malignancy of the biliary tract and the 5th most common malignancy of the gastrointestinal tract, with an incidence of 2.5 cases per 100,000 population per year.<sup>40-44,47-59</sup> The incidence has reported to vary considerably worldwide and even within the same country among

different ethnic groups.<sup>32</sup> Higher rates are found in Chile, Mexico, Bolivia, and Japan, while in the USA, Hispanic Americans and southwestern Native Americans are affected more frequently.<sup>32</sup> Gallbladder carcinoma has been reported to be found in 1% to 2% and 0.1% of open and laparoscopic cholecystectomies, and causes 6,500 deaths annually in the USA.<sup>50-54</sup> It is a disorder primarily of the elderly (mean age, 65 years; 90% are in their 6th decade or older).<sup>50</sup> About 10% of gallbladders removed from patients more than 65 years of age harbor invasive carcinoma. This malignancy occurs more frequently in women (2-3:1), and cholelithiasis is found in 70%-90% of patients.<sup>27</sup> The risk of carcinoma developing in a patient with cholelithiasis is only 1%-3%, but the risk appears to be higher when the stones are larger than 3 cm in diameter. Other associated conditions, which account for a minority of cases of gallbladder carcinoma, include porcelain gallbladder,<sup>21,26,47,60-69</sup> mirizzi syndrome,<sup>47</sup> choledochal cyst,<sup>29,55-57</sup> ulcerative colitis,<sup>47</sup> primary sclerosing cholangitis,<sup>19</sup> familial adenomatous polyposis or Gardner's syndrome<sup>40</sup> and peutz Jeghers syndrome.<sup>27,41</sup> Since this study has not probed into the etiological and detailed clinical factors, these associations were not analyzed here. There was only one study from the Kingdom of Saudi Arabia, which has reported the rate of gallbladder carcinoma to be only 0.5%. In our study this rate was 0.95%, close to the lower value of range reported from the USA.<sup>32</sup> A comparative analysis was carried out with 7 other studies published in the Kingdom of Saudi Arabia.<sup>3,10,12,36-38</sup> Results from all these studies were quite similar.

In conclusion, the rate of gallbladder diseases and stones are high and these reports from other parts of Kingdom of Saudi Arabia are suggesting that the problem is so common that it deserves a large scale population based study to get a more accurate picture.

## References

- Gollan JL, Bulkley GB, Diehl AM. National Institutes of Health consensus development conference statement on gallstones and laparoscopic cholecystectomy. *Am J Surg* 1993; 165: 390-398.
- Craplin MK, Jenkinson LR, Kassab JY. Management of gallstones in a district general hospital. *Br J Surg*; 1985; 72: 428-432.
- Ahmed AF, El-Hassan OM. Gallstones revisited? Al-Madinah Al-Mounawarrah's Experience. *Saudi Med J* 1993; 14: 436-439.
- Bayoumi RA, Abu Zeid YA, Abdul Sadig A, Awad Elkarim O. Sickle cell disease in sudan. *Trans R Soc Trop Med Hyg* 1988; 82: 164-168.
- El-Hazim MA. Clinical manifestation and laboratory findings of sickle cell anaemia in association with alpha-thalassaemia in Saudi Arabia. *Acta Haematol* 1985; 74: 155-160.
- Cook GC. Serum cholestrol concentration in Arabs in Riyadh Saudi Arabia, and it relation to adult hypolactasia. *Trop Geogr Med* 1976; 28: 339-342.
- Rawas M, Baksh T, Noorwali A, Merdad A. Percutaneous cholecystostomy and gallstones dissolution by MTBE. *Saudi Med J* 1990; 11: 25-28.
- Baksh T, Nasif O, Noorwali M, Rawas M. Non surgical ablation of the gall bladder: an animal study. *Saudi Med J* 1993; 14: 138-141.
- Hadidy S, Turki J, Misri HT. Cholelithiasis in the Syrian population *Am J Surg* 1987; 153: 392-393.
- Mofti AB, Al-Tameem MM, Al-Khudairy NN. Experience with elective Cholecystectomy in King Khalid University Hospital. *Annals of Saudi Medicine* 1987; 7: 107-110.
- Tamimi TM, Wosornu L, Al-Khozaim A, AbdulGhani A. Increased cholecystectomy rates in Saudi Arabia. *Lancet*. 1990; 336:1235-1237.
- Ahmed AF, Osman MH, Mahmood ME. Risk factors for gallstone formation in young Saudi women: a case control study. *Annals of Saudi Medicine* 1993; 12: 395-399.
- Gibney EJ. Asymptomatic gallstones. *Br J Surg* 1990; 77: 368-372.
- Bateson MC. Gallstone surgery in Scotland. *Lancet* 1988; 2: 1250-1258.
- Barbra L, Sama C, Morselli Labate AM. A population study on the prevalence of gallstone disease: the sirmione study. *Hepatology* 1987; 7: 913-917.
- Grundy SM, Klaser SC. Highlights of the meeting on prevention of gallstones. *Hepatology* 1987; 136: 725-727.
- Little JM, Avramovic J. Gallstone formation after major abdominal surgery. *Lancet* 1991; 337: 1135-1137.
- Khetin U, Dwarakanath S, Pinson CW, Jenkins RL, Arkin CF. Histopathology of the donor gallbladder removed at orthotopic liver transplantation: correlation with graft function. *Hum Pathol* 1991; 22: 437-441.
- Fox JG, Dewhirst FE, Shen Z. Hepatic Helicobacter species identified in bile and gallbladder from Chileans with chronic cholecystitis. *Gastroenterology* 1998; 114: 755-763.
- Blaser MJ. Helicobacters and biliary tract disease. *Gastroenterology* 1998; 114: 840-845.
- Ashur H, Sieeal B, Oland Y, Adam YG. Calcified gallbladder (porcelain gallbladder). *Arch Surg* 1978; 113: 594-596.
- Dabbs DJ. Eosinophilic and lympho-eosinophilic cholecystitis. *Am J Surg Pathol* 1993; 17: 497-501.
- Chitkara YK. Pathology of the gallbladder in common bile duct obstruction: the concept of ascending cholecystitis. *Hum Pathol* 1993; 24: 279-283.
- Jessurun J, Bolio-Solis A, Manivel JC. Diffuse lymphoplasmacytic acalculous cholecystitis: a distinctive form of chronic cholecystitis as-associated with primary sclerosing cholangitis. *Hum Pathol* 1998; 28: 512-517.
- Shimizu M, Miura J, Tanaka T, Itoh H, Saitoh Y. Porcelain gallbladder: relation between its type by ultrasound and incidence of cancer. *J Clin Gastroenterol* 1989; 11: 471-476.
- Estrada RL, Brown NM, James CE. Chronic follicular cholecystitis: radiological, pathological and surgical aspects. *Br J Surg* 1960; 48: 205-209.
- Stephens S, Sternberg. "Diagnostic Surgical Pathology" 3rd ed. Philadelphia (PA): Lipponcott Williams and Wilkins; 1999.
- Feldman M, Sleisenger MH. Scharschmidt BP editors. Sleisenger and Fordiran Gastrointestinal and liver diseases: 6th ed. Philadelphia: WB Saunders: 1998. p. 948-972.
- Redaelli CA, Buchler MW, Schilling MK. High incidence of Mirizzi syndrome and gallbladder carcinoma. *Surgery* 1997; 121: 58-63.
- Johnston DE, Kaplan MM. Pathogenesis and treatment of gallstones *N Engl J Med* 1993; 328: 412-421.

31. Kmiot WA, Perry EP, Donovan IA. Cholesierolosis in patients with chronic acalculous biliary pain. *Br J Surg* 1994; 81: 112-115.
32. Albores-Saavedra J, Henson DE, Sobin LH. Histological typing of tumors of the gallbladder and extrahepatic bile ducts. In: World Health Organization international classification of tumors. 2nd ed. New York: Springer-Verlag; 1991.
33. Albores-Saavedra J, Vardaman CJ, Vuitch F. Non-neoplastic polypoid lesions and adenomas of the gall bladder. In: Rosen PP, Fechner RE. editors. *Norwalk: Appleton and Lange Pathology Annual*; 1993. (Pt 1): 145-177.
34. Yamigawa H. Intestinal metaplasia-dysplasia-carcinoma sequence of the gallbladder. *Acta Pathol* 1986; 36: 989-997.
35. Kozuka S, Hachisuka K. Incidence by Age and Sex of intestinal metaplasia in the gall bladder. *Hum Pathol* 1984; 15: 779-784.
36. Hamour OA, Kashgari RH, Al Harbi MA. Minimal invasive surgery: a district hospital. *East Afr Med J* 1998; 75: 274-278.
37. Dempsey EF, Ericsson H, Al-Shareef Z. Laproscopic Cholecystectomy: A Tabuk Experience. *Saudi Med J* 1993; 14: 429-431.
38. Mokhtar AM. Cholelithiasis in the western region of Saudi Arabia. *East Afr Med J* 1990; 67: 286-290.
39. Yamaguchi K, Enjoji M. Gallbladder polyps: inflammatory, hyperplastic and neoplastic types. *Surg Pathol* 1988; 1: 203-213.
40. Walsh N, Qizilbash A, Banerjee J, Waugh GA. Biliary neoplasia in Gardner's syndrome. *Arch Pathol Lab Med* 1987; 111: 6-77.
41. Wada K, Tanaka M, Yamaguchi K, Wada K. Carcinoma and polyps of the gallbladder associated with Peutz-Jeghers syndrome. *Digital Discovery in Science* 1987; 32: 943-946.
42. Banletl DL, Fong Y, Former JG, Brennan MF, Blumgan LH. Long-term results after resection for gallbladder cancer: implications for staging and management. *Ann Surg* 1996; 224: 639-646.
43. Young RH, Scully RE. Ovarian metastases from carcinoma of the gallbladder and extrahepatic bile ducts simulating primary tumors of the ovary: a report of 6 cases. *Int J Gynecol Pathol* 1990; 9: 60-72.
44. Kronic A, Martinovic N, Calonje E, Milinkovic M. Cutaneous metastatic adenocarcinoma of gallbladder origin presenting as carcinoma of unknown primary. *Int J Dermatol* 1995; 34: 360-362.
45. Bateson MC. Cholecystectomy in Saudi Arabia [letter comments]. *Lancet* 1990; 336: 1505.
46. Albores-Saavedra J, Nadji M, Henson DE. Intestinal-type adenocarcinoma of the gallbladder a clinicopathologic and immunohistochemical study of seven cases. *Am J Surg Pathol* 1986; 10: 19-25.
47. Weedon D. Diseases of the gallbladder. In: MacSween RMN, Anthony PP, Scheuer PJ, Bun AD, Portmann BC, editors. *Pathology of the liver*. 3rd ed. New York: Churchill Livingstone; 1994. p. 513-534.
48. Albores-Saavedra J, Henson DE. Tumors of the gallbladder and extra-hepatic ducts. In: Hanman WH, editors. *Atlas of tumor pathology*. 2nd series. fascicle 22. Washington DC: Armed Forces Institute of Pathology; 1986.
49. Piehler JM, Crichlow RW. Primary Tumors of gallbladder. *Surg Obstet* 1978; 147: 929-942.
50. Jones RS. Carcinoma of the gallbladder. *Surg Clin North Am* 1990; 70: 1419-1427.
51. Pin HA, Dooley WC, Yeo CJ, Cameron JL. Malignancies of the biliary tree. *Curr Prob Surg* 1995; 32: 1-90.
52. Yamaguchi K, Chijiwa K, Ichimiya H. Gallbladder carcinoma in the era of laparoscopic cholecystectomy. *Arch Surg* 1996; 131: 981-985.
53. Sandor J, Ihasz M, Fazekas T, Regoly-Merei J, Batorfi J. Unexpected gallbladder cancer and laparoscopic surgery. *Surg Endosc* 1995; 9: 1207-1210.
54. Carriaga MT, Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. *Cancer* 1995; 75: 171-190.
55. Misra SP, Dwivedi M. Pancreaticobiliary ductal union. *Gut* 1998; 31: 1144-1149.
56. Ohta T, Nagakaw AT, Ueno K. Clinical experience of biliary tract carcinoma associated with anomalous union of the pancreaticobiliary ductal system. *Jpn J Surg* 1990; 20: 36-43.
57. Komi N, Tamura T, Miyoshi Y, Kunitomo K, Ldaka H, Takehara H. Nationwide survey of cases of choledochal cyst: analysis of coexistent anomalies, complications and surgical treatment in 645 cases. *Surg Gastroenterol* 1984; 3: 69-73.
58. Dodd LG, Moffatt J, Hudson ER, Layfield LJ. Fine-needle aspiration of primary gallbladder carcinoma. *Diagn Cytopathol* 1996; 15: 151-156.
59. Zargar SA, Khuroo MS, Mahajan R, Jan GM, Shah P. Laproscopic-guided fine needle aspiration biopsy of gallbladder masses. *Radiology* 1991; 179: 275-278.
60. Yamaguchi K, Enjoji M. Carcinoma of the gallbladder a clinicopathology of 103 patients and a newly proposed staging. *Cancer* 1988; 62: 1425-1432.
61. Jawad AJ, Kurban K, EL-Bakry A, Al Rabeeah A, Seraj K. Laparoscopic cholecystectomy for cholelithiasis during infancy and child hood: cost analysis and review of current indications. *World J Surg* 1998; 22: 69-74.
62. Bilhartz LE. Acute acalculous cholecystitis, adenomyomatosis, cholesterolosis, and polyps of the gallbladder. In: Feldman M, Sleisenger MH, Scharshmidt BF. editors. *Sleisenger and Fordtran's gastrointestinal and liver disease: pathophysiology diagnosis and management*. 6th ed. Philadelphia: WB Saunders; 1998: p. 993-1005.
63. Sahlin S, Stahlberg D, Einarsson K. Cholesterol metabolism in liver and gallbladder mucosa of patients with cholesterolosis. *hepatology* 1995; 21: 1269-1275.
64. Cetia F, Lombardo F, Malei PF. Black pigment gallstones with cholesterol gallstones in the same gallbladder: 13 cases in a surgical series of 1,226 patients with gallbladder stones. *Digital Discovery in Science* 1995; 40: 534-538.
65. Malet PF, Dabezies MA, Huang G, Long WB, Gadc TR, Soloway RD. Quantitative infrared spectroscopy of common bile duct stones. *Gastroenterology* 1988; 94: 1217-1221.
66. Kirm MH, Sekijima J, Lee SP. Primary intrahepatic stones. *Am J Gastroenterol* 1995; 90: 540-548.
67. Crowther RS, Soloway RD. Pigment gallstone pathogenesis: from man to molecules. *Semin Liver Dis* 1990; 10: 171-180.
68. Singelton JM. Calcific enterolith obstruction of the intestine. *Br J Surg* 1970; 57: 234-236.
69. Csendes A, Burdiles P, Maluenda F, Diaz JC, Csendes P, Mitru N. Simultaneous bacteriologic assessment of bile from gallbladder and common ile duct in control subjects and patients with gallstones and common duct stones. *Arch Surg* 1996; 131: 389-394.