# Prevalence and risk factors of gallstone disease in a high altitude Saudi population

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## معدل انتشار حصيات المرارة وعوامل اختطارها بين السعوديِّين القاطنين في المُرْتَفَعات

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**الخلاصة:** درس الباحثون معدل انتشار مرض حصيات المرارة وعوامل اختطارها بين السعوديِّين، في دراسة مجتمعية مستعرضة شملت 291 مواطناً من مقاطعة أبها في منطقة عسير. وقد جمعت المعطيات الأساسية المتعلِّقة بجميع المساهمين في الدراسة، وأُجريت لهم دراسة بالأمواج فوق الصوتية للناحية العليا من البطن لكشف حصيات المرارة. وقد بلغ معدل انتشار حصيات المرارة 11.7٪. وعند تحليل النتائج بالتحوُّف اللوجستي المتعدِّد المتغيِّرات، اتَّضح أن عوامل الاختطار التي يُعْتَدُّ بها إحصائياً للإصابة بحصيات المرارة هي الأنوثة، والسوابق العائلية لحصيات المرارة وسوابق الإصابة بالتهاب البنكرياس. أما العمر، والتعليم، وضغط الدم، والتدخين، وتناوُل القهوة، والبدانة، والسكَّري، وعدد الأحمال واستخدام مانعات الحمل بالفم، فلم تكن من عوامل الاختطار التي يُعْتَدُّ بها إحصائياً. وقد أظهر التحليل التفاضلي للأعراض أن الآلام في الـمَرَاقّ اليُمنَى تترافق ترافقاً يُعْتَدُّ به إحصائياً بحصيات المرارة.

ABSTRACT To study the prevalence of gallstone disease and related risk factors in a Saudi Arabian population a cross-sectional community-based study was made of 291 people from Abha district, Asir region. A structured interview collected background data and all participants had upper abdominal ultrasonography to detect gallstones. The overall prevalence of gallstone disease was 11.7%. Using logistic regression multivariate analysis, the following were significant risk factors for gallstone disease: female sex, family history of gallstone disease and past history of pancreatitis. Age, education, blood pressure, smoking, coffee intake, overweight, diabetes mellitus, number of pregnancies and use of oral contraceptives were not significant risk factors. Discriminant analysis of symptoms showed that only right hypochondrium pain was significantly associated with gallstone disease.

**Prévalence et facteurs de risque de la lithiase biliaire dans une population saoudienne de haute altitude**

RÉSUMÉ Afin de déterminer la prévalence et les facteurs de risque de la lithiase biliaire dans une population saoudienne, il a été mené une étude transversale en population générale à partir de 291 habitants du district d'Abha, dans la région d'Asir. Un entretien structuré a permis la collecte des données fondamentales et tous les participants ont subi une échographie abdominale visant à détecter la présence de calculs biliaires. La prévalence globale de la lithiase biliaire était de 11,7 %. L'analyse de régression logistique multiple a montré que le sexe féminin, une histoire familiale de lithiase biliaire et des antécédents de pancréatite étaient des facteurs de risque de lithiase biliaire significatifs. L'âge, le niveau d'instruction, la pression artérielle, le tabagisme, la consommation de café, le surpoids, le diabète sucré, le nombre de grossesses et la contraception orale ne sont pas apparus comme des facteurs de risque significatifs. L'analyse discriminante des symptômes a révélé que seule la douleur de l'hypochondre droit était associée de manière significative à la lithiase biliaire.

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## Introduction

Asir region (population 1 200 000) is located in the southwest of Saudi Arabia covering an area of more than 80 000 km$^2$. The region extends from the high mountains of Sarawat (with an altitude of 3200 m above sea level) to the Red Sea, and lies a few kilometers from the northern border of neighbouring Yemen. The region is divided into 15 health districts. Primary health care services in Abha health district are provided through a widespread network of 36 urban and rural primary health care centres, providing services to 129 465 people. Each primary health care centre has a well-defined catchment area and population.

Gallstone disease is a major cause of morbidity, and sometimes mortality, throughout the world. About 320 cholecystectomies are performed every year in Asir Central Hospital, an affiliated teaching hospital with 550 beds. This only reflects the magnitude of symptomatic gallstone disease in our region. However, in other reports, more than 70% of individuals had asymptomatic gallstone disease [*1,2*]. The change in lifestyle among Saudis in recent years may suggest that the condition is of increasing health importance.

The prevalence of gallstone disease has been little studied on a community basis in Saudi Arabia. Therefore, we decided to study the prevalence of gallstone disease and related risk factors in Abha region at a community level.

## Methods

### Sample

The minimum sample size required for the study was calculated to be 264 cases, with an anticipated population proportion of 20%, and with an absolute precision of 5% at 95% confidence interval [*3*]. To avoid loss of cases, a total of 300 cases was planned to be collected. They were selected using a cluster sampling technique from the catchment areas of the 36 primary health care centres in Abha region. To ensure equal involvement of adult males and females in the study, couples were regarded as the study unit. Through house-to-house survey, couples were contacted and asked to attend their local primary health care centre.

### Data collection

At the primary health care centre couples were interviewed using a structured observation and interview questionnaires to collect data about sociodemographic factors, habits, past history of right hypochondrial pain, pancreatitis or any other diseases, and family history of diseases, especially gallstone disease. History of pancreatitis was obtained by reviewing case records (based on feedback of results of prior referral to hospital, serum amylase and lipase results and/or positive findings on ultrasonography) [*4*].

Blood pressure was measured at least twice, in a controlled environment, after at least 3 to 5 min of rest in the seated position. The subject was asked to sit exposing his/her arm then using a sphygmomanometer and stethoscope the systolic pressure was recorded when the first Korotkoff sound appeared while the diastolic pressure was recorded when the sound disappeared in Korotkoff phase V. The average of 2 readings was recorded. WHO definitions were used as the cut-off for hypertension: systolic blood pressure > 140 mmHg and/or diastolic blood pressure > 90 mmHg [*5*].

Height was measured to the nearest 0.1 cm using measuring tape and weight was measured using a standardized measuring scale to the nearest 0.1 kg. Body mass index (BMI) was calculated and overweight was defined as BMI $\geq$ 25 kg/m$^2$ [*6*].

Upper abdominal ultrasonography examination was performed on each person for detection of gallstone disease. Ultrasonography remains the method of choice for the diagnosis of gallstone disease, offering a number of advantages: it is non-invasive, there is no ionizing radiation, it is relatively inexpensive and adjacent organs can also be assessed. It also has a high sensitivity (97%), specificity (93.6%) and diagnostic accuracy (93.0%) [*7*]. Ultrasonography provides better results than computerized tomography and similar results to those of perioral cholecystography in determining the number and diameter of the stones. The sensitivity of ultrasonography in diagnosing gallbladder stones is comparable to magnetic resonance cholangiography (97.7%) [*7*].

### Analysis

Data were coded, validated and analysed using *SPSS* PC + software package, version 13. Univariate analysis methods were used at the 5% level of significance. Multivariate logistic regression analysis was used to identify potential risk factors. Kappa statistics were calculated to measure agreement between symptoms and ultrasonography findings. To study the reliability and validity of symptoms (as mentioned by respondents) and ultrasonography findings in detecting gallstone disease, stepwise discriminant analysis was used.

## Results

A total of 291 persons (response rate 97%) were included in the present study (143 males and 148 females). Age range was 25–85 years with a mean of 44.3 [standard deviation (SD) = 10.2] years and a median of 43.0 years. The mean age of males [48.6 years (SD = 10.3)] was significantly higher than that of females [40.3 years (SD = 8.4)] ($t = 7.529$, $P < 0.05$).

A total of 34 cases had positive findings of gallstone disease by ultrasound (4 cases had already had cholecystectomy and 30 had gallstones). There were 6 males and 28 females. The overall prevalence of gallstone disease was 11.7% [95% confidence interval (CI): 8.4–15.7]. The prevalence in males and females was 4.2% (95% CI: 1.7–8.5) and 19.9% (95% CI: 13.2–25.8) respectively.

Among positive gallstone cases, a single stone was found in 19 cases (63.3%), and thick-walled gallbladders were found in 5 cases (16.7%). Furthermore, 26 cases (86.7%) with stones were newly discovered, of which 16 (61.5%) had one or more symptoms suggestive of gallstone disease, and only 10 (38.5%) were asymptomatic.

Table 1 shows the agreement of symptoms with ultrasonography findings. Right hypochondrial pain was found to be significantly associated with positive ultrasonography findings for gallstone disease ($\kappa = 0.148$, $P = 0.002$).

The results of discriminant analysis of symptoms reported by respondents are shown in Table 2. Only right hypochondrial pain was significantly associated with gallstone disease (a low value of Wilks $\lambda$, canonical correlation and $P < 0.05$). This symptom had a high sensitivity and specificity of more than 70% in detecting gallstone disease.

In univariate analysis, gallstone disease was common among females, illiterate patients, smokers and those aged > 40 years. It was also common among people having a past history of pancreatis and family history of gallstone disease.

Using logistic regression multivariate analysis (Table 3), it was clear that people with a past history of pancreatitis were 11 times more likely to have gallstone disease (adjusted OR = 11.5; 95% CI: 7.1–15.5) than people with no history of pancreatitis. Similarly, the following factors were also

Table 1 **Agreement of gallbladder symptoms with ultrasonography findings**

| Symptom | No. of patients | Prevalence of gallstone disease (%) | Agreement κ-statistic | *P*-value |
|---|---|---|---|---|
| Jaundice | 14 | 14.3 | 0.106 | 0.074 |
| Right hypochondrium pain | 95 | 20.0 | 0.148 | 0.002* |
| Flatulence | 149 | 16.1 | 0.089 | 0.062 |
| Dyspepsia | 132 | 15.2 | 0.068 | 0.093 |

**Significant (P < 0.05).*

identified as significant risk factors for gallstone disease: female sex (adjusted OR = 4.2; 95% CI: 1.3–13.6) and family history of gallbladder stones (adjusted OR = 3.4; 95% CI: 1.3–8.7). On the other hand, age, education, blood pressure, smoking, coffee intake, overweight, diabetes, number of pregnancies and use of contraceptives among females were not significant.

## Discussion

Cholecystectomy is one of the most common operations performed in general surgical units throughout Saudi Arabia. It comprises about 47% of major and 23% of total general surgical operations in our hospital in Abha city and 15%–50% of all laparotomies in 2 different studies from Medina city [*1,8*]. These data give the impression that gallstone disease is common among Saudi Arabians. However, apart from a few scattered reports on gallstone disease from different parts of Saudi Arabia [*1,8–12*], the prevalence of gallstone disease at the country level has not been determined yet. Whereas the prevalence of gallstone disease in our series was 11.7%, it was 4.4% in a study group of 1604 pregnant women from Al Kharj Military Hospital [*11*]. In other parts of the world, varying figures were given for the prevalence of gallstones,

Table 2 **Discriminant analysis model: potential association of symptoms (as reported by respondents) with gallbladder stones (ultrasonography findings)**

| Symptom | Wilks λ | Canonical correlation | *F*-statistic | % patients correctly classified Sensitivity % | Specificity % | Overall % |
|---|---|---|---|---|---|---|
| Jaundice | 0.986 | 0.063 | 4.004 | 15.8 | 44.6 | 47.7 |
| Right hypochondrium pain | 0.218 | 0.175 | 9.603* | 71.3 | 74.8 | 72.4 |
| Flatulence | 0.981 | 0.081 | 3.867 | 50.8 | 21.6 | 52.9 |
| Dyspepsia | 0.991 | 0.051 | 2.823 | 43.1 | 49.2 | 47.7 |

**Significant (P < 0.05).*

Table 3 **Multivariate logistic regression model: adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of potential risk factors in developing gallbladder stones**

| Variable | No. screened | % positive | Adjusted OR | 95% CI |
|---|---|---|---|---|
| *Age (years)* | | | | |
| < 40 | 103 | 9.7 | | |
| 40+ | 188 | 12.8 | 1.39 | 0.57–3.40 |
| *Education* | | | | |
| Educated | 179 | 7.8 | | |
| Illiterate | 112 | 17.9 | 1.68 | 0.69–4.12 |
| *Hypertension* | | | | |
| Normotensive | 265 | 12.1 | | |
| Hypertensive | 26 | 7.7 | 0.57 | 0.06–5.03 |
| *Smoking habit* | | | | |
| Non-smoker | 258 | 10.9 | | |
| Smoker | 33 | 18.2 | 1.61 | 0.29–8.95 |
| *Coffee intake* | | | | |
| No | 203 | 11.3 | | |
| Yes | 88 | 12.5 | 1.07 | 0.45–2.55 |
| *Diabetes mellitus* | | | | |
| Non-diabetic | 248 | 12.1 | | |
| Diabetic | 43 | 9.3 | 0.435 | 0.11–1.77 |
| *Sex* | | | | |
| Male | 143 | 4.2 | | |
| Female | 148 | 18.9 | 4.24 | 1.32–13.58* |
| *Family history of gallbladder stones* | | | | |
| No | 255 | 9.4 | | |
| Yes | 36 | 27.8 | 3.41 | 1.32–8.78* |
| *History of pancreatitis* | | | | |
| No | 287 | 10.8 | | |
| Yes | 4 | 75.0 | 11.52 | 7.06–15.54* |
| *Obesity* | | | | |
| BMI < 25 kg/m$^2$ | 64 | 9.4 | | |
| BMI $\geq$ 25 kg/m$^2$ | 217 | 12.9 | 1.46 | 0.53–4.24 |

**Significant (P < 0.05).*
*BMI = body mass index.*
*OR = odds ratio; CI = confidence interval.*

ranging from 4% to more than 20% (Tunisia 4.1%, Islamic Republic of Iran 4.7%, Bangladesh 5.4%, Peru 10.7%, Germany 7.8%, New Zealand 20.8% and United States of America 10%–15%) [*13–19*].

It is known that the pathogenesis of gallstone disease is related to imbalance

in the metabolic and dynamic process of cholesterol and bile acids. This can be directly influenced by genetic, hormonal and metabolic factors. Although the association between gallstone disease and "fat, fertile, female and forty" has been observed and taught for a long time, it has a limited support in formal epidemiological studies [*10*]. It has been known that female sex, race, obesity, diabetes mellitus, ageing, cirrhosis, type IV hyperlipidaemia, parity, oral contraceptive use, smoking, and family history of gallstone disease are risk factors for gallstone formation [*1,2,11,12,20–28*]. In our study, only female sex and family history of gallstone and/or past history of pancreatitis were found to be significant risk factors. These findings agree with the findings in other national reports, although some of them added other risk factors including obesity, BMI > 30 kg/m$^2$ and parity [*1,9–12*]. This inconsistency could be attributed to the environmental and genetic differences among different societies.

Few studies have sought to describe the prevalence of gallstones in high altitude communities. Moro et al., in their study of gallstone disease in high altitude Peruvian rural populations (> 3000 m above sea level), reported that high altitude was not a positive risk factor for gallstone disease [*16*]. On the other hand, Spathis et al. [*29*] reported high rates of gallstones among high altitude villagers of Ladakh, India. They attributed this rate to slow intestinal transit time that can lead to constipation, increased bilirubin absorption and higher bile concentrations in the gallbladder [*16,29*]. In addition, increased blood cell formation and hence increased haemolysis may increase levels of bilirubin pigments with an increased risk of pigment gallstones [*30*]. Our region is one of the highest altitude regions in the Middle East (> 3000 m above sea level). This may be one of the etiological factors contributing to the high prevalence in our area, but it is difficult to draw firm conclusions without a comparative study between high and low altitude areas in this regard.

In contrast to similar reports from America and Europe, where more than two thirds of gallstones were asymptomatic [*19,23*], more than 60% of our cases had symptoms. The low prevalence of symptomatic gallstones in cross-sectional surveys from the industrialized countries is probably due to rapid diagnosis and treatment [*31*]. Controversies exist about the management of asymptomatic gallstones, particularly in the era of laparoscopic surgery [*32–35*]. Nearly 10% of individuals with asymptomatic gallstones may develop symptoms or complications requiring treatment within 5 years [*36*].

We found that female sex, history of right hypochondrium pain, family history of gallstone disease, and/or past history of pancreatitis, were significantly associated with gallstone disease and this agrees with other reports [*9,37*]. It has also been reported that acute pancreatitis seen in Asir region is predominantly biliary and more frequent in females [*38*].

Although gallstone disease has complications, the treatment (cholecystectomy) has its own risks as well. Complications of gallstone disease range from simple recurrent biliary colic to severe, life-threatening ascending cholangitis and/or pancreatitis. Carcinoma of the gallbladder had been postulated to be intimately associated with long-standing gallstone disease, particularly when large or numerous cholesterol gallstones are present and in elderly female patients [*39,40*]. Furthermore, gallstone disease is thought to be a risk factor for pancreaticobiliary cancer, particularly in patients with choledocholithiasis [*41*].

Most decision analysis studies do not favour prophylactic cholecystectomy for asymptomatic cholelithiasis. Nonetheless, many studies have listed certain criteria for carrying out elective cholecystectomy in asymptomatic patients, including: life expectancy > 20 years, calculi > 3 cm in diameter, particularly in individuals in geographical regions with a high prevalence of gallbladder cancer or calculi < 3 mm, chronically obliterated cystic duct, non-functioning gallbladder and calcified (porcelain) gallbladder. This, in turn, has given rise to a great deal of controversy regarding the optimal management of asymptomatic or "silent" gallstones. While cholecystectomy is the undisputed gold standard treatment for symptomatic gallstones, the natural history of silent gallstones is not known well enough to recommend a definitive therapeutic strategy for such patients. The treatment options for asymptomatic or silent gallstones range from no treatment to selective cholecystectomy in the at-risk group to elective cholecystectomy in all patients. There are a large number of proponents for each of these options so each merits careful consideration [*42*].

In conclusion, gallstone disease is prevalent in the community of Asir region of Saudi Arabia (11.7%). Primary health care physicians in the region should pay more attention to patients with right hypochondrial pain, especially if they are women, with family history of gallstone disease and/or having a past history of pancreatitis. They should be referred for upper abdominal ultrasonography for screening and early detection of gallstone disease. We would like to emphasize that a fundamental knowledge of gallstone disease and its complications is essential for clinicians. Thus, high-risk groups might be identified and a realistic approach for prophylaxis for any reversible risk factors could then be offered.

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### *References*

1. Ahmed AF, El-Hassan OM, Mahmoud ME. Risk factors for gallstone formation in young Saudi women: a case control study. *Annals of Saudi medicine*, 1992, 12(4):395–9.
2. Hopper KD et al. The prevalence of asymptomatic gallstones in the general population. *Investigative radiology*, 1991, 26(11):939–45.
3. Lwanga SK, Lemeshow S, eds. *Sample size determination in health studies*. Geneva, World Health Organization, 1990.
4. Doherty G, ed. *Essentials of diagnosis and treatment in surgery*. New York, McGraw-Hill, 2005.
5. *Hypertension control. Report of a WHO Expert Committee 1996*. Geneva, World Health Organization, 1996 (WHO Technical Report Series, No. 862).
6. *Obesity: preventing and managing the global epidemic. Report of a WHO consultation on obesity, 3–5 June 1997*. Geneva, World Health Organization, 1997 (WHO/NUT/NCD/98.1).

7. Gandolfi L et al. The role of ultrasound in biliary and pancreatic diseases. *European journal of ultrasound*, 2003, 16:141–59.

8. Ahmed AF et al. Gallstones revisited? Almadinah Almounawarah's experience (a prospective study of 212 consecutive cases). *Saudi medical journal*, 1993, 14(5):436–9.

9. Mokhtar AMA. Cholelithiasis in the western region of Saudi Arabia. *East African medical journal*, 1990, 67(4):286–90.

10. Murshid KR. Symptomatic gallstones: a disease of young Saudi women. *Saudi journal of gastroenterology*, 1998, 4(3):159–62.

11. Modawi SS, Abu Khader MM. Prevalence of gallstones in a pregnant Saudi population. *Saudi medical journal*, 1995, 16(4):304–7.

12. Chiedozi LC et al. Cholelithiasis in young Saudi women. *East African medical journal*, 1998, 75(3):184–7.

13. Safer L et al. Epidemiologie de la lithiase biliaire dans le centre de la Tunisie [Epidemiology of cholelithiasis in central Tunisia]. *Gastroentérologie clinique et biologique*, 2000, 24(10):883–7.

14. Massarrat S. Prevalence of gallstone disease in Iran. *Journal of gastroenterology and hepatology*, 2001, 16(5):564–7.

15. Dhar SC et al. Gallstone disease in a rural Bangladeshi community. *Indian journal of gastroenterology,* 2001, 20(6):223–6.

16. Moro PL et al. Gallstone disease in Peruvian coastal natives and highland migrants. *Gut*, 2000, 46(4):569–73.

17. Kratzer W et al. Pravalenz der Cholezystolithiasis in Suddeutschland—eine sonographische Untersuchung an 2.498 Personen einer landlichen Bevolkerung. [Prevalence of cholecystolithiasis in South Germany—an ultrasound study of 2,498 persons of a rural population.] *Zeitschrift für Gastroenterologie*, 1999, 37(12):1157–62.

18. Chapman BA et al. Gallstone prevalence in Christchurch: risk factors and clinical significance. *New Zealand medical journal,* 2000, 113(1104):46–8.

19. Browning JD, Horton JD. Gallstone disease and its complications. *Seminars in gastrointestinal disease*, 2003, 14(4):165–77.

20. La Vecchia C et al. Risk factors for gallstone disease requiring surgery. *International journal of epidemiology*, 1991, 20(1):209–15.

21. Nakeeb A et al. Gallstones: genetics versus environment. *Annals of surgery*, 2002, 235(6):842–9.

22. Mittal B, Mittal RD. Genetics of gallstone disease. *Journal of postgraduate medicine*, 2002, 48(2):149–52.

23. Acalovschi MV et al. Risk of asymptomatic and symptomatic gallstones in moderately obese women: a longitudinal follow-up study. *American journal of gastroenterology*, 1997, 92(1):127–31.

24. Pagliarulo M et al. Gallstone disease and related risk factors in a large cohort of diabetic patients. *Digestive and liver disease*, 2004, 36(2):130–4.

25. Bartoli E, Capron JP. Epidemiology and natural history of cholelithiasis. *La Revue du praticien*, 2000, 50(19):2112–6.

26. Chapman BA et al. Prevalence of gallbladder disease in diabetes mellitus. *Digestive diseases and sciences*, 1996, 41(11):2222–8.

27. Fornari F et al. Incidence of gallstones in a population of patients with cirrhosis. *Journal of hepatology*, 1994, 20(6):797–801.

28. Stampfer MJ et al. Risk of symptomatic gallstones in women with severe obesity. *American journal of clinical nutrition*, 1992, 55(3):652–8.

29. Spathis A et al. Gallstones in a community free of obesity but prone to slow intestinal transit. *European journal of gastroenterology & hepatology*, 1997, 9:201–6.

30. Trotman BW et al. Hemolysis-induced gallstones in mice: increased unconjugated bilirubin in hepatic bile predisposes to gallstone formation. *Gastroenterology*, 1981, 81:232–6.

31. Heaton KW et al. Symptomatic and silent gallstones in the community. *Gut*, 1991, 32(3):316–20.

32. Gibney EJ. Asymptomatic gallstones. *British journal of surgery*, 1990, 77(4): 368–72.

33. Meshikhes AW. Asymptomatic gallstones in the laparoscopic era. *Journal of the Royal College of Surgeons of Edinburgh*, 2002, 47(6):742–8.

34. Coelho JC et al. Laparoscopic cholecystectomy to treat patients with asymptomatic gallstones. *Digestive surgery*, 2000, 17(4):344–7.

35. Mentes BB et al. Gastrointestinal quality of life in patients with symptomatic or asymptomatic cholelithiasis before and after laparoscopic cholecystectomy. *Surgical endoscopy*, 2001, 15(11):1267–72.

36. Halldestam I et al. Development of symptoms and complications in individuals with asymptomatic gallstones. *British journal of surgery*, 2004, 91(6):734–8.

37. Festi D et al. Clinical manifestations of gallstone disease: evidence from the multicenter Italian study on cholelithiasis (MICOL). *Hepatology*, 1999, 30(4):839–46.

38. Abu-Eshy SA. Pattern of acute pancreatitis. *Saudi medical journal*, 2001, 22(3):215–8.

39. Vitetta L et al. Gallstones and gallbladder carcinoma. *Australian and New Zealand journal of surgery*, 2000, 70(9):667–73.

40. Zahrani IH, Mansoor I. Gallbladder pathologies and cholelithiasis. *Saudi medical journal,* 2001, 22(10):885–9.

41. Bansal P, Sonnenberg A. Comorbid occurrence of cholelithiasis and gastrointestinal cancer. *European journal of gastroenterology and hepatology*, 1996, 8(10):985–8.

42. Gupta SK, Shukla VK. Silent gallstones: a therapeutic dilemma. *Tropical gastroenterology*, 2004, 25(2):65–8.