# Epidemiology and risk factors for gallstones in the paediatric and adult population in the city of Al-Ahsa

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July 9, 2021


## Abstract

Background and Aims: Cholelithiasis is a common upper gastrointestinal tract disorder in the Kingdom of Saudi Arabia. Analyses of risk factors for gallstone formation may explain the need for lifestyle modifications. Therefore, our aim was to identify sex- and age-related differences in the prevalence and risk factors for gallstones among Saudi individuals in the city of Al-Ahsa. Methods: The medical records of patients, [?]1 year of age, with a radiologically confirmed diagnosis of gallstones, between 2014 through 2016, were retrieved and relevant demographic and clinical data extracted. Risk factors for cholelithiasis for all age groups were identified. Results: A total of 618 patients had radiologically confirmed gallstones over the 3-year period of observation. The prevalence was higher among females than males (73% versus 27%, respectively) in all age groups. In the paediatric group, the prevalence of gallstones was higher among girls with obesity and those with sickle cell disorders. Advanced age, a higher body mass index, high low-density lipoproteins, triglycerides, and cholesterol were independently associated with cholelithiasis in both gender of all age groups. Hepatitis B and C were not found to be risk factors for cholelithiasis. Conclusions: Older age, female sex, a high body mass index, and hyperlipidaemia are major risk factors for gall stones formation among all age groups. Haemolytic anaemia, namely sickle cell disease, is a prevalent risk factor in paediatric population.


## Introduction

An imbalance in the chemical constituents of bile components can result in the formation of gallstones of varying size and shape[1]. Cholesterol supersaturation, gallbladder dysfunction and nucleation defect play key roles in the pathogenesis of gallstone formation [2]. Gallstones are classified into pure cholesterol stones, pigment stones, and mixed composition stones [1,2]. Cholesterol stones are yellow in colour, more commonly found in adults, and might dissolve with bile acid therapy [3]. Pigment stones are classified into brown or black types. Black pigment stones are more common in patients with liver cirrhosis or chronic haemolytic anaemias[4].

Epidemiological studies have revealed geographical influences on the prevalence rate of gallstones [5,6]. Worldwide, there appears to be higher rates of cholelithiasis in Western Caucasian, Hispanic, and Native American populations, with the rates being lower among East European, African American, and Asian populations[6].

The prevalence of gallstones in the Kingdom of Saudi Arabia (KSA), however, has not been well established to date and may in fact vary from region to region across the KSA [7]. In 2007, community-based study of the Asir region of the KSA, Abu-Eshy et al. reported a prevalence rate of 11.7% [8]. In 2014, Alawad et al. reported a prevalence rate of 10.9% in the Hail region of the northern KSA. [9]. A screening of 1018 patients by using ultrasound, identified a prevalence rate of 23% in the city of Al Madina. [10]. A cross sectional study performed in the city of Riyadh in 2017 reported a prevalence rate of gallstones of 8.6% [11].

Numerous adult studies have reported an association between the development of cholesterol gallstones and the following factors: obesity, a western diet, type 2 diabetes, metabolic syndrome, advanced age, female sex, parity, rapid weight loss, oestrogen therapy, total parenteral nutrition, genetic factors, and ethnicity[12]. By contrast, pigmented stones are principally caused by haemolytic blood disorders, such as sickle cell disease. The highest estimated prevalence of sickle cell disease in the KSA is in the eastern region [13]. A premarital screening program identified a prevalence rate in adult population for sickle cell trait (SCT) of 17% and 1.2% for sickle cell disease (SCD), while a new born screening program reported 21% for SCT and 2.6% for SCD in eastern province [14]. Considering that 50-85% of patients with sickle cell anaemia will develop pigmented gallstones [15], the population of Al-Ahsa, a large oasis located in the eastern province of the KSA, would be at highest risk for gallstones in the KSA [16].

Our aim in this study was to identify the prevalence and risk factors for gallstones in the city of Al-Ahsa, based on age and sex and to find if haemolytic anemia is a risk factor in all age group. To the best of our knowledge, no previous study has systematically analysed the relationship between sex- and age-related risk factors and gallstone formation.

## Methods and Materials

Statement of ethics

The study protocol was approved by International Medical Research Centre Scientific Committee (SP 17/036/A), and the Institutional Review Board (IRBC/354/17).

Study design

We conducted a retrospective chart review among patients, [?]1 year of age, with radiologically confirmed cholelithiasis at King Abdul Aziz Hospital (KAH) in the city of Al-Ahsa. The data collected for three consecutive years, 2014, 2015, and 2016, using electronic and manual medical records. Excluded were patients under the age of 1 year, as well as those with primary anatomic abnormalities of biliary system, with ultrasound confirming biliary sludge without gall stones, and patients with incomplete data.

The following demographic (age, sex, weight, and height) and biochemical parameters (lipid profile, serum amylase level, hepatitis B and C serology, sickle cell test, and electrophoresis) were extracted from the charts. Medical and social histories were screened for medication, smoking, alcohol use, and the presence of other comorbidities, such as diabetes and thyroid disease. For analysis, patients were classified based on their age and body mass index (BMI). Age was classified into the following three groups: group 1, 0-18 years; group 2, 19-60 years; and group 3, >60 years. The World Health Organization (WHO) classification of BMI was used, as follows: overweight, 25[?]0–29[?]9 kg/m2, or obese, [?]30 kg/m2.

Sample size was calculated using the following formula: N= (Z1-Alpha) 2 x (pq)/E. For this sample size calculation, we used the previously published prevalence rate of cholelithiasis among Saudi population of 11.7% [8], at power of 0.80 and margin of error of 0.05. Taking into consideration a rate of missing variables in the medical charts of 50%, a sample size of 480 patients would be necessary to identify predictive factors for gallstones. After screening, we included 636 patients in our study group.

Statistical analysis

Descriptive statistics (mean and standard deviation, or count and frequency) were used for the following variables: sex and age distribution; height, weight and the calculated BMI; hepatitis B and C status; presence or absence of sickle cell disorders; total serum levels (with normal cut offs indicated) of cholesterol ([?]5.2 mmol/L), high-density lipoproteins (HDL, 1.0-1.3 mmol/L), low-density lipoproteins (LDL, [?]2.59 mmol/L), amylase (40-140 U/L), and triglyceride (TG, [?]1.7 mmol/L); and thickness of the gall bladder wall (<3 mm).

Multivariate logistic regression analyses were used to identify significant independent risk factors for cholelithiasis. The odds ratio (OR), and associated 95% confidence interval (CI), for cholelithiasis was calculated for each independent factor, adjusted for sex and age. p value <0.05 was considered significant.

All analyses were performed using SPSS (version 20, IBM, Chicago, IL, USA).

## Results

Of the 643 patients, with radiological confirmation of gallstones, enrolled into our study, 25 patients were excluded due to missing data, with the final analysis being based on the data of 618 patients, 185 males and 433 females. The age, gender, and BMI distribution of our study cohort is shown in Table 1.

The following groups were formed for analysis: group 1, 45 paediatric patients, with a mean age of 12.2±7.08 years of girls and 12.6±5.52 years for boys; group 2, 509 middle-age adults, with a mean age of 38.7±10.4 years for women and 37.9±10.4 for men; and group 3, 64 older patients (>60 years of age), with a mean age of 71.6±8.13 for women and 73.8±9.99 years for men.

**Distribution by BMI**

The distribution of patients in each age group (groups 1 through 3) by BMI classification is shown in Table 1. About 42% of patients in group 1 (paediatric group) were obese (BMI [?]30 kg/m2) and 20% were overweight (BMI, 25-29.9 kg/m2). In group 2 (middle-age adults), 55% were obese and about 34% were overweight. In group 3 (older patients), 44% were obese and 37.5% were overweight. Across all three groups, a BMI [?]30 kg/m2 (obese) was more frequent among females than males, respectively, as follows: group 1, 45.4% versus 33%; group 2, 58% versus 48.7%; and group 3, 46% versus 40%. These sex-specific differences in the proportion of obese individuals were all significant.

**Distribution by lipid profile**

The distribution of patients in each age group by their lipid profile is shown in Table 2. Of note, this information was available for a smaller number of patients in each age group, as follows: 14 patients in group 1 (paediatric), 212 in group 2 (middle-age adults), and 34 in group 3 (older patients).

In group 1, 57% of patients had a high cholesterol level, with 43% having a high TG level in each gender. HDL levels were low in 14.3% of males and 43% of females tested in group 1, with LDL levels being high in 28.6% of males and 57% of females tested.

In group 2, lipid profiles were available for 69 of the 148 male patients; high cholesterol level was identified in 83%, and high TG level in 86%. LDL level was high in 55%, and a HDL level <1.3 mmol/L in 72.5%. For women, lipid profiles were available for 143 of 361 patients enrolled, with high cholesterol identified in 94%, with high TGs in 93%, high LDL in 73%, and low HDL in 50%.

In group 3, lipid profiles were available in 11 of 25 men, with 91% of these men having high cholesterol, 82% had a TG level >1.7 mmol/l, 55% LDL >2.59 mmol/L, and 64% a HDL <1.3 m mol/L. Lipid profiles were available in 23 of the 39 women in this group, with 70% of these women having high cholesterol, 74% high TG values, 74% high LDL, and 65% low HDL.

**Proportion of the population with haemolytic anaemia**

The prevalence and distribution of haemolytic anaemia is shown in Table 3. In group 1, 25% of boys and 30% of girls tested positive for sickle cell disease. In group 2, this proportion decreased 5.8%, with no significant differences between-sex, while in group 3, of the 40 patients who underwent testing, only 1 man tested positive.

**Distribution by viral hepatitis status**

The distribution of patients who tested positive for HBV or HCV is shown in Table 3. None of the 20 patients in group1 tested positive for HBV, and only 1 girl had positive serology for HCV. In group 2, HBV screening was performed in 378 patients, with a positive serology in 9 patients (2.4%). HCV screening was performed in 267 patients, with a positive serology identified in 2 women (1%). In group 3, none of the patients tested showed positive serology for HBV; while for HCV, of the 34 women tested, a positive serology was identified in 3 (8.8%).

**Complications and outcome of gallstones**

With the exception of 43 patients, all others required cholecystectomy. Cholecystectomy was performed laparoscopically in the majority of patients, with only 4 required an open approach, with one of these being a case of conversion from laparoscopic to open. Bariatric surgery was performed at the same time in 6 patients. Post-cholecystectomy recovery was unremarkable in all patients, with no significant morbidity and no incidence of mortality.

At time of presentation, biliary pancreatitis, with high serum amylase level, was evident in half (50%) of the females and 44% of the males in group 1 (paediatric). In group 2, 65% of 100 males, compared to 55% of 210 females, presented with an elevation of serum amylase. In group 3, a high serum amylase level was identified in 87.5% of males and 72% of females.

Cholecystitis, identified by a thickening of the gall bladder wall (GBWT) on ultrasound, was identified in 5 children (one male 8.3% and 4 females 12.1%), compared to 72% of women and 8% in Men in group 2. 28% of women and 18% of men in group 3 showed GBWT.

**Comparison of risk factors among males and females Table-4**

In the male population, the binary multivariate logistic regression analyses showed significant association of gall stone with the following variables; advancing age (OR 0.403, 95% CI 0.23-0.72, P=0.002), Obesity (OR 0.51, 95% CI 0.32-0.83, P=0.006), triglycerides (OR 0 .464, 95% CI 0.257-0.837,P=0.011), LDL (OR 1.683, 95%CI 1.159-2.445, P=0.006); sickle cell anemia (OR15.31, 95% CI 3.60- 65.04, P=0.001). While no significant association with Total cholesterol (OR1.024, 95% CI 0.649- 1.616, P=0. 91) and HDL (OR0.639, 95% CI 0.140-2.909, P= 0.563).

Hepatitis B and hepatitis C were not found to be correlated with the prevalence of gall stones (p>0.05).

In the female population, the binary multivariate logistic regression analyses showed **advancing age** of 19-60 years (OR 2.484, 95% CI 1.39-4.43, P<0.002), increased **BMI** (OR 1.95, 95% CI1.393- 4.431, P<0.006); **elevated total serum cholesterol** (OR=2.657 CI of 0.999-7.067 P=0.050) ;**triglycerides** (OR 2.156, CI 1.194 -3.892,P=0 .011),**HDL** (OR 2.57, CI 1.086- 6.109 , P=0.032); **LDL** (OR 5.478, CI 1.348-22.261, P=0.017) and sickle cell anemia (OR16.786, CI 3.965-71.064, P <0.0001) were significantly associated with the risk of cholelithiasis.

Hepatitis B and C were not significantly correlated with prevalence of gall stones (p>0.05). (Table-3)

## Discussion

The rising prevalence of gallstone disease in the Saudi population is a cause of concern. In 1990, an increase in the frequency of cholecystectomy in the eastern province of the KSA was noticed, which reflect the increase in the incidence of gallstones[17]. Transabdominal ultrasound provides the ideal diagnostic tool to accurately determine the prevalence of gallstone disease; a sit is a safe imaging technique with high sensitivity and specificity for gallstones [6]. In our study, we included patients with a diagnosis of gallstones confirmed by transabdominal ultrasound at KAH in Al-Ahsa city, over 3 consecutive years to evaluate the prevalence and sex- and age specific risk factors for cholelithiasis. The KAH is one of the Ministry of National Guard hospitals in the KSA that provides primary, secondary, and tertiary healthcare services to National Guard employees and their families, as well as eligible Saudi citizens referred from other hospitals. It has a total bed capacity of about 300 beds. Annually about 220cholecystectomies are performed in our hospital, with 10% being paediatric cases. This is comparable to the data for King Fahad Hospital in Almadinah Almounawarah, with a 500-bedcapacity, where 400 cholecystectomies are performed on average per year[18].We note that we excluded patients under the age of 1 year from our study as the aetiology of cholelithiasis in infants is unique, generally being related to congenital anatomical disorders, genetic diseases, ceftriaxone therapy, and total parenteral nutrition [19]. Gallstones in infancy can present with cholestasis, pale stools, sepsis, and abdominal pain but, more often, is asymptomatic and resolves spontaneously without surgical intervention [20]. Our findings of a higher prevalence of gallstones in females than males agree with previously published international observations which reported a 2-fold higher increase in the risk for gallstones in women compared to men[21-22-23]. Similarly, a higher prevalence among women than men has been reported for the KSA[8-9-10-11]. The underlying pathophysiology for gall stone formation in women could be related to effects of sex hormones on bile secretion and function of the gall bladder; this is supported by a specifically higher risk of gallstone formation after menopause and in post-menopausal women using oestrogen therapy[24-25-26]. These findings related to cholesterol stones, with the prevalence of pigmented stone being almost equal among both sex in countries where pigmented stone is more prevalent, as in Taiwan [27]. Female sex was also found to be a risk factor for gallstones in children, where 73% of cases in our paediatric population were girls. Again, this finding agrees with previously published data [28]. Obesity and overweight are well recognized for their strong association with gallstone disease. People with obesity have a higher incidence of cholelithiasis, cholecystitis, and cholesterolosis compared to lean individuals [29]. In our study group, obesity was a strong risk factor for gallstone formation in both paediatric and adult patients. Our findings also suggest that the epidemic of obesity in Saudi children has contributed significantly to the striking increase in paediatric gallstone disease. This concurs with the findings of Mehta et al. who reported that a strong association between paediatric gall bladder cholelithiasis and obesity (P=0.03) [28]. In our study a higher BMI among adults was the most important preventable risk factor that appears to largely account for the high prevalence of gallstone (Pvalue 0.05). In good agreement with our study, Hung et al., in their population-based case control study, reported obesity to be a strong predictor for the development of gallstones (OR 1.89, 95%CI 1.18-3.04, Pl=0.008), with women being at a higher risk for gallstones than men (OR 1.91, 95%CI 1.07-3.41, P=0.030 )[30]. Analogous findings were reported by in a Mendelian randomized study that showed that an increase BMI among women was a causative factor for cholelithiasis (P=0.001) [31]. It has been reported that 20-30% of all gallstones in children are due to haemolytic diseases such as sickle-cell disease, hereditary spherocytosis and thalassemia [32]. In 40-50% of paediatric cases, the underlying cause of gallstones is due to another known aetiology, including total parenteral nutrition, prolonged fasting, ileal disease or ileal resection, frusemide therapy, congenital biliary diseases, such as a choledochal cyst, chronic liver disease and progressive familial intrahepatic cholestasis (PFIC). Around 30-40% of cases are idiopathic in nature [20].

Gallstone is a common complication in children with haemoglobinopathies because of the recurrent episodes of haemolysis leading to an increase in bilirubin excretion and pigment gallstones formation. The development of pigment gallstones in patients with sickle cell disease is largely age-dependent, with 15% of cases being in children <10 years of age, 22% in children 10-14 years of age, and 36% in children 15-18 years of age, with a reported prevalence of 50% by the age of 22 years[33]. Our study findings revealed a noteworthy relationship between gallstone formation and sickle cell anemia among paediatric patients, with girls being at higher risk than boys (30.3% versus 25%). The findings from the Howard University Centre for Sickle Cell Disease study agreed with our findings, with gallstones reported in 70.6% of girls with sickle cell anaemia, compared to 55.1% in boys[34]. While Dooki et al. reported a lower rate of cholelithiasis among children with haemolytic anaemia of 13.6[35], Chabchoub et al from Tunisia reported similar prevalence to our study with 36.8% of paediatric patients with gallstones had haemolytic anaemias. [36]. By contrast, in our adult group, males with sickle cell disorders were at a higher risk for gallstones than females. A retrospective review by Martin et al. [37] reported that 25.7% of adult patients with sickle cell disease presented with an increased incidence of gallstone formation. Analogous findings were reported by Gumerio et al., with an incidence rate of gallstone formation of 45% among patients with sickle cell-haemoglobin C disease and heterozygous sickle cell disease/beta-thalassemia (Sβ), with the average age of onset of cholelithiasis in this group being 12.5 years[38]. Laparoscopic cholecystectomy is the treatment of choice in children with clinically symptomatic disease, with the best treatment option for asymptomatic cases being a source of debate [39]. As an example, whereas the Brazilian study [37] and the Jamaican study[40] recommended conservative management for asymptomatic children due to lack of significant complications over a period of observation of 8 years, other investigators still recommend elective cholecystectomy as the gold standard therapy in children with sickle cell disease with asymptomatic cholelithiasis to prevent potential complications, such as cholecystitis and choledocholithiasis, as well as postoperative complications (sickle cell crisis) when emergency cholecystectomy is performed [37].

In our analyses, high serum cholesterol (p=0.027), TG (P=011), and LDL (P=0.006), and low HDL (P=0.03) were associated with a higher risk of gallstones, particularly among women. These findings were in good agreement with previous cross-sectional and prospective investigations[41,42]. A population-based study conducted in China by Andreotti et al. [42] reported that high serum levels of TG and low levels of HDL were associated with an elevated risk for biliary stones, as well as biliary tract cancer. Malik et al. [43] agreed that the prevalence of cholelithiasis was higher among women than men with a hyperlipidaemic profile (80% versus 71.42%). This study also revealed that hypercholesteremia was the most common abnormality in both sexes, followed by hypertriglyceridemia, and that lipid profiles improved up to 6 months after cholecystectomy, but that HDL remained unchanged. A spectrometric study further supported these findings, reported a linear correlation between high cholesterol and the rate of gallstones (P=0.05), with a similar linear correlation for LDL levels (P< 0.001) [44]. Bhatti et al. reported strong relationship between gallstone formation and a fatty liver, particularly among adult females [41]. The occurrence of cholelithiasis was not associated with either hepatitis B or C infection in our study. Analogous findings were reported in a systemic literature review, indicating a null relationship between hepatitis B infection and cholelithiasis [45]. Of note, a community-based study in Taiwan did report a positive linear relationship between gallstone formation and hepatitis C, but not B, among males[46]. Our findings could be explained by the fact that the prevalence of hepatitis B is rapidly declining in the KSA due to the premarital screening program and efficacy of the immunization program by our national health organization. Finally, we did identify that 13.4% of our patients in the 2015 had type 2 diabetes, with a comparable prevalence rate of 10% in 2016. We note that 25.5% of patients in both years used Calcium and vitamin D supplementation for not less than 2 months prior to surgery. Data for 2014 was incomplete regarding this information.

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