Ultrasound Detected Asymptomatic Cholelithiasis: An Age-based Protocol for Management

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ABSTRACT

Objective: This study was undertaken to examine the correlation between age and gender and the presence of ultrasound findings of acute or chronic cholecystitis in adult patients with cholelithiasis.

Method: The demographic data of all patients diagnosed with cholelithiasis and chlolecystis on ultrasound between January 1, 2002 and December 31, 2006 were reviewed and statistically analysed. 2

Results: Five hundred adults, 373 females (74.6%) and 127 males (25.4%), were diagnosed with cholelithiasis during the five-year period. Ages ranged from 18 to 94 years with a median age of 47 years. The diagnosis for cholecystitis was equivocal in 11 patients. Of the remaining 489, 22.1% (108) were diagnosed as positive for cholecystitis by ultrasound, the remaining 77.9% (381) being negative.

Keywords: Asymptomatic, cholelithiasis, management

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No association was found between gender and cholecysytitis in bivariate analysis, ($\chi^2 = 1.82$, df =1, p = 0.177). A statistically significant relation was found between age group category and ultrasound-determined cholecystitis status ($\chi^2 = 32.58$, df = 4, $p < 0.001$). Higher proportions of persons in the 20−39-year (40.9%) and 40−59-year (20.4%) age groups had cholecystitis on ultrasound examination compared to other age categories where corresponding rates were approximately 11% or less.

Conclusion: Patients 60 years or older who were diagnosed with cholelithiasis on ultrasound examination were less likely to have cholecystitis than younger patients.

INTRODUCTION

Cholelithiasis is a common disorder. Schirmer *et al* reported that the disease and its sequelae are the most costly gastrointestinal disease in the United States of America (USA). Some 500 000 cholecystectomies are done per year and 30% of patients with asymptomatic cholelithiasis will warrant surgery during their lifetime. Factors increasing the likelihood of surgical intervention include the size of stones, presence of haemolytic anaemia and a non-functioning gallbladder (1).

Ultrasound is a safe, rapidly performed examination with high sensitivity and specificity for cholelithiasis. The introduction of ultrasonography has resulted in an increased rate of diagnosis of asymptomatic gallstones which has created a therapeutic dilemma.

Wada *et al* in Japan found that only 20% of 680 asymptomatic patients followed for 10 to 17 years developed biliary symptoms. They found that in all age groups, approximately 70% of patients were asymptomatic (2).

Angelico *et al* in Italy reported results of a ten-year longitudinal study on a random sample of 426 females in which 76.9% were asymptomatic at initial diagnosis. Of these, 15.4% experienced at least one episode of biliary pain; 23.1% were submitted to elective cholecystectomy and 61.5% remained aymptomatic (3).

Various authors have sought to address this clinical issue with recommendations based on data from their population. The general consensus is that cholecystectomy is too aggressive an approach for asymptomatic gallstones, however, criteria for conservative management have not been fully resolved (4−8). In their review, Picci *et al* cited epidemiological cross-sectional screening studies showing that 66 to 77% of patients with gallstones are

asymptomatic (9). The prevalence of cholelithiasis is variable between ethnic groups as well as among members of the same ethnic group in different geographic locations so it is not possible to extrapolate findings from one group to another (10, 11). Within any given population, age and gender are logical parameters with which to start reviewing statistical correlation of a disease.

Acute and chronic cholecystitis are the common sequelae of cholelithiasis. This retrospective study was undertaken to determine the statistical relationships between age and gender and the presence on ultrasound of the most common sequelae of cholelithiasis.

SUBJECTS AND METHODS

A retrospective review was done of all patients diagnosed with cholelithiasis at the University Hospital of the West Indies, Kingston, Jamaica, during the period January 1, 2002 to December 31, 2006. Data were obtained by review of the Report database of the Radiology Department.

The reports were reviewed to determine the presence of acute or chronic cholecystitis. The data were analysed for significance using bivariate analysis, binary logistic regression, odd's ratios, Nagelkerke's R^2 test and Hosmer and Lemeshow test.

RESULTS

All patients with diagnosis of cholelithiasis on ultrasound during the five-year period January 1, 2002 to December 31, 2006 were stratified for diagnosis of cholecystitis status. Five hundred and thirty-two subjects were diagnosed with cholelithiasis. Of these, 32 were children (*ie* persons below 18 years of age). Of the remaining 500 adult records, the female to male ratio was almost 3:1; females – 74.6% and males – 25.4 %. Table 1 summarizes the basic demographic characteristics of the adult study subjects. Adult ages ranged from 18 to 94 years. The median age was 47 years, interquartile range 34−66 years. The majority of persons (37.1%, 189) was in the 20−39 years age group with slightly more than a quarter (134 and 131) being in the 40−59 and the 60−79-year age groups, respectively. For 11 adults, ultrasound results were equivocal or indeterminate. Consequently, there were 489 individuals for whom definitive ultrasound diagnoses were available. Of the 489 adults, 22.1% (108) were diagnosed as positive for cholecystitis by ultrasound, the remaining 77.9% (381) being negative. In bivariate analysis, no association between gender and cholecystitis was found (χ^2 =1.82, df = 1, p = 0.177). Among males, 17.7 % (22 of 124) were positive for cholecystitis by ultrasound while 23.6% (86 of 365) were so deemed among females. A statistically significant relation was found between age group category and ultrasound-determined cholecystitis status (χ^2 = 32.58, df = 4, p < 0.001). Higher proportions of persons in the 20−39-year age group (40.9%) and 40−59-year age group (20.4%) had cholecystitis on ultrasound examination compared to other age categories where corresponding rates were approximately 11% or less. The results of a binary logistic regression model to predict ultrasonographic diagnosis

of cholecystitis among these participants with gallstones using gender and age-group as categorical covariates are shown in Table 2.

Similar to findings in bivariate analysis, in this population, gender was not a significant predictor of cholecystitis status on ultrasound examination. Age on the other hand was a significant predictor. Persons in the age category 20−39 years were about nine times as likely to be positive for cholecystitis on ultrasound as those 80 years or older (OR = 8.9; 95% CI = 2.1, 38.1). Using 80 years or older as the reference category, the other age categories had neither a statistically significant elevated nor reduced risk for cholecystitis. Nagelkerke's R^2 was 0.105 suggesting that only about 11% of the variance in cholecystitis status was explained by gender and age. Model fit was good as assessed by the Hosmer and Lemeshow test (*p*-value = 0.998). Prediction success overall was 77.9% with the model being more useful for predicting negative status than positive status (100% for negative and 0% for positive).

DISCUSSION

The major finding in this study of patients with cholelithiasis is the statistically significant relationship between age group category and ultrasound-determined cholecystitis status.

Patients in age groups 20–39 years and 40–59 years were more likely to have cholecystitis than other patients. For patients in the 20–39-year age group, the increased tendency was statistically significant compared to the patients older than 80 years ($p < 0.003$). This finding appears to correlate with the classic description of cholecystitis as a disease of fat, fertile, forty-year old females.

In the pre-ultrasound era, it would not have been possible to routinely detect, on incidental examinations, the many instances of patients with asymptomatic cholelithiasis because only 10–20% of gallstones calcify and become visible on plain X-ray.

We have identified only one other study which suggests that younger patients are more likely to have sequelae of cholelithiasis; Heaton *et al* in a review of 1896 British adults found that in both sexes, the age at cholecystectomy was on average nine years less than the age at which silent stones were detected (12).

Our findings suggest that, with respect to risk of subsequent cholecystitis, it may be possible to defer cholecystectomy for stones found incidentally on ultrasound with no features of sequelae in persons above the age of 60 years if, on clinical review, the patients are asymptomatic.

Conservative management of cholelithiasis must also factor in risk of other sequelae such as gallbladder carcinoma and pancreatitis.

Randi *et al* have reviewed gallbladder cancer worldwide. They conclude that it is a relatively rare neoplasm with high incidence in certain populations in India, Pakistan and Chile (13). They postulated that aetiology varied between countries but found a history of gallstones to be the strongest risk factor.

We have no data for Jamaica but in Japan, Inui *et al* reported that the incidence of gallbladder tumours had been increasing (14). In response, the Japanese have instituted ultrasonographic screening for the presence of polyps and tumours. Mihara *et al* reported a detection rate of 0.011% (143 cases) for gallbladder cancer in mass screening of 1 306 947 persons (15). Using resected gallbladder specimens as the gold standard, Jang *et al* in South Korea reported sensitivites of 90% for high resolution ultrasound (HRUS) in the diagnosis and staging of gallbladder cancer. High resolution ultrasound was more sensitive than both multidetector computed tomography and endoscopic ultrasonography (16).

Pancreatitis is a severe complication of gallstone disease with significant mortality. Venneman *et al* have demonstrated that small gallstones may increase the risk of pancreatitis (17). They reported that patients with pancreatitis had more and smaller stones than patients with uncomplicated gallstones. In a review of 5000 patients, they concluded that "prophylactic cholecystectomy may lead to gain or loss of life-years in patients with small stones, depending on incidence and mortality of pancreatitis".

A possible limitation of this study is the sensitivity and specificity of ultrasound for the diagnosis of cholecystitis and whether stones which are uncomplicated on ultrasound are indeed asymptomatic. Ultrasound is not as sensitive as cholescintigraphy for diagnosing acute cholecystitis (18, 19) but if

screening criteria combine normal ultrasound with clinical evaluation, these limitations might be overcome.

A previous study conducted by some authors of this paper indicated that there was no significant difference in the mean age for males and females with cholelithiasis both being approximately 50 years (20). In this study, there was no association between gender and cholecystitis on bivariate analysis. Further, age and gender contributed only 11% to the variance of cholecystitis in this population. The findings suggest that other factors such as number and size of stones, body mass index (BMI) and associated medical conditions may be important in the development of cholecystitis. These should be the subject of a prospective study. Collection of information on other variables and putative risk factors for cholecystitis and their subsequent inclusion in the logistic regression model may provide further insight on significant predictors of cholecystitis on ultrasound examination among individuals with gallstones. The future inclusion of these factors has the potential to improve the prediction success concerning cholecystitis positive cases. Increased sample size might further help elucidate study findings. This would help clarify the marginal situation that exists in the age group 40−59 years that had a *p*-value of 0.050. Additionally, there would be increased precision around the estimates of the significant odds ratio which is currently relatively wide.

In conclusion, we reviewed instances of cholecystitis in patients with cholelithiasis. The significant finding was that age predicted the occurrence of cholecystitis. Patients between the ages of 20–60 years are more likely to have cholecystitis. We suggest that asymptomatic gallstones found on incidental examination of patients 60 years or older may be managed by clinical monitoring and intermittent ultrasound review. The other significant finding is

that age and gender explain only 11% of cholecystitis status in the population studied so a prospective study should be undertaken to assess other factors such as BMI and co-morbid conditions in the development of cholecystitis.

REFERENCES

1. Schirmer BD, Winters KL, Edlich RF. Cholelithiasis and cholecystitis. J Long Term Eff Med Implants 2005; **15:** 329−38.

2. Wada K, Wada K, Imamura T. Natural course of asymptomatic gallstone disease. Nippon Rinsho 1993; **51:** 1737−43.

3. Angelico F, Del Ben M, Barbato A, Conti R, Urbinati G. Ten-year incidence and natural history of gallstone disease in a rural population of women in central Italy. The Rome Group for the Epidemiology and Prevention of Cholelithiasis (GREPCO). Ital J Gastroenterol Hepatol 1997; **29:** 249−54.

4. Honoré LH. Increased incidence of symptomatic cholesterol cholelithiasis in perimenopausal women receiving estrogen replacement therapy: a retrospective study. J Reprod Med 1980; **25:** 187.

5. Sakorafas GH, Milingos D, Peros G. Asymptomatic cholelithiasis: is cholecystectomy really needed? A critical reappraisal 15 years after the introduction of laparoscopic cholecystectomy. Dig Dis Sci 2007; **52:** 1313−25.

6. Gupta SK, Shukla VK. Silent gallstones: a therapeutic dilemma. Trop Gastroenterol 2004; **25:** 65−8.

7. Elías Pollina J, Delgado Alvira R, Martínez-Pardo NG, Ros Mar L, Calleja Aguayo E, Esteban Ibarz JA. Must we change the surgical treatment of gallstones? Cir Pediatr 2008; **21:** 96−9.

8. Bogue CO, Murphy AJ, Gerstle JT, Moineddin R, Danemanet A. Risk factors, complications, and outcomes of gallstones in children: a single-center review. J Pediatr Gastroenterol Nutr 2010; **50:** 303−8.

9. Picci R, Perri SG, Dalla Torre A, Pietrasanta D, Castaldo P, Nicita A et al . Therapy of asymptomatic gallstones: indications and limits. Chir Ital 2005; **57:** 35−45.

10. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. Gastroenterology 1999; **117:** 632−9.

11. Stinton LM, Myers RP, Shaffer EA. Epidemiology of gallstones. Gastroenterol Clin North Am 2010; **39:** 157−69, vii.

12. Heaton KW, Braddon FE, Mountford RA, Hughes AO, Emmett PM. Symptomatic and silent gall stones in the community. Gut 1991; **32:** 316−20.

13. Randi G, Franceschi S, La Vecchia C. Gallbladder cancer worldwide: geographical distribution and risk factors. Int J Cancer 2006; **118:** 1591−602.

14. Inui K, Yoshino J, Miyoshi H. Diagnosis of gallbladder tumors. Intern Med 2011; **50:** 1133−6. Epub 2011 Jun 1.

15. Mihara S, Yoshioka R, Tamada M, Nagano K, Tanaka S, Hirano S et al. Update of ultrasonographic screening for gallbladder cancer in mass survey. Tanto Sui 2005; **26:** 801−4.

16. Jang JY, Kim SW, Lee SE, Hwang DW, Kim EJ, Lee JY et al. Differential diagnostic and staging accuracies of high resolution ultrasonography, endoscopic ultrasonography, and multidetector computed tomography for gallbladder polypoid lesions and gallbladder cancer. Ann Surg 2009; **250:** 943−9.

17. Venneman NG, Renooij W, Rehfeld JF, VanBerge-Henegouwen GP, Go PM, Broeders IA et al. Small gallstones are associated with increased risk of acute pancreatitis: potential benefits of prophylactic cholecystectomy? Am J Gastroenterol 2005; **100:** 2540−50.

18. Chatziioannou SN, Moore WH, Ford PV, Dhekne RD. Hepatobiliary scintigraphy is superior to abdominal ultrasonography in suspected acute cholecystitis. Surgery 2000; **127:** 609−13.

19. Kalimi R, Gecelter GR, Caplin D, Brickman M, Tronco GT, Love C. Diagnosis of acute cholecystitis: sensitivity of sonography, cholescintigraphy, and combined sonography-cholescintigraphy. J Am Coll Surg 2001; **193:** 609−13.

20. West WM, Brady-West DC, West KP, Frankson M. Cholelithiasis on imaging – an analysis of clinical presentations by age and gender in a Jamaican population. West Indian Med J 2009; **58:** 375−8.

Table 1: Participant characteristics

Variable		**% (n)**
Gender (n =500)		
	Male	25.4% (127)
	Female	74.6% (373)
Age (n =500)		
	< 20 years	1.8% (9)
	20−39 years	37.8% (189)
	40−59 years	26.8% (134)
	60−79 years	26.2% (131)
	≥ 80 years	7.4% (37)
Cholecystitis status on ultrasound (n = 489, 11 indeterminate/equivocal excluded)		
	Positive	22.1% (108)
	Negative	77.9% (381)

Table 2: Odds ratios for cholecystitis on ultrasound obtained by logistic regression

Predictor Variable	**B**	**S.E**	***p*-value**	**OR (95% Confidence Interval)**
Gender (Female)	0.179	0.276	0.515	1.2 (0.7−2.1)
Age group				
< 20 years	0.76	1.29	0.553	2.1 (0.17−26.7)
20−39 years	2.18	0.74	0.003*	8.9 (2.1−38.1)*
40−59 years	1.49	0.76	0.050	4.4 (1.0 −19.6)
60−79 years	0.74	0.78	0.341	2.1 (0.5−9.7)

- Cholecystitis status on ultrasound: positive coded as 1, negative as 0
- Gender: Female = 1, male = 0 (reference category)
- Age: Age category 80 years and over used as reference category
- * = statistically significant