

Natural history of asymptomatic gallstones: differential behaviour in male and female subjects

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ABSTRACT

Objective: The natural history of asymptomatic (silent) gallstones has been inadequately studied. Existing information derives from studies based on oral cholecystography or relatively small sample sizes. We planned a retrospective cohort study in subjects with gallstones to determine conversion rates from asymptomatic to symptomatic.

Methods: We extracted data from computerised databases of one government hospital and two private clinics in Malaysia. Files were scrutinised to ensure that criteria for asymptomatic gallstones were fulfilled. Patients were called on telephone, further questioned to confirm that the gallstones at detection were truly asymptomatic, and asked about symptoms that were consistent with previously defined criteria for biliary colic. Appropriate ethical clearances were taken.

Results: 213 (112 males) patients fulfilled the criteria for asymptomatic gallstones and could be contacted. 23 (10.8%) developed pain after an average follow up interval of 4.02 years (range 0.1-11 years). Conversion rates from asymptomatic to symptomatic gallstones were high in the first two years of follow up, averaging 4.03 ± 0.965 per year. Over time the conversion rates slowed, and by year 10 the annual conversion rate averaged only 1.38 ± 0.29 . Conversion rates were much higher for females compared to males (F:M hazard ratio 3.23, SE 1.54, $p > z$ 0.014). The lifetime risks for conversion approached 6.15% for males, and 22.1% for females.

Conclusion: In conclusion, asymptomatic gallstones are much more likely to convert to symptomatic in females than in males. Males in whom asymptomatic stones are discovered should be advised conservative treatment. Surgery may be preferable to conservative management if the subject is a young female.

KEY WORDS:

Cholelithiasis, asymptomatic conditions, natural history, biliary colic, cohort studies

INTRODUCTION

The prevalence of gallstones is 5-10%, and rises with age.¹⁻⁴ Although the prevalence varies widely,⁵⁻⁸ the information is often ultrasound (US)-based and reliable. Unfortunately we have less dependable information on the behaviour of the disease. About 70% of gallstones are asymptomatic,⁹ but we do not reliably know how many turn symptomatic. This is because some of the literature on the natural history of gallstones derives from studies in which gallstones were diagnosed using oral cholecystography (OCG).¹⁰ OCG has an accuracy barely higher than 50%,¹¹ and has been rendered virtually obsolete by US, where the accuracy exceeds 95%.¹² US-based studies do exist, but the numbers have been small: large numbers are difficult to achieve in prospective cohort studies. Most studies have comprised fewer than 100 subjects.^{8,13} Consequently, it has been difficult for surgeons to advice individuals who present with asymptomatic gallstones. Some reports favour conservative management,^{8,14} but there are contrary opinions as well.¹⁵

We planned a retrospective cohort study to determine if we could get a better understanding of the natural history of asymptomatic gallstones.

MATERIALS AND METHODS

Patients were identified from radiology records of Hospital Selayang, Selangor, and from two private clinics in Kuala Lumpur. Radiologists were asked to retrieve information on subjects with asymptomatic gallstones. The entire databases were scanned. The subjects were contacted and telephonically queried about complications of gallstones.

From Hospital Selayang, cases from 2001-2010 were identified from the computerised database. Since Hospital Selayang is fully computerised, it was possible to also examine outpatient data for all cases to understand the indication for the sonography. Records were reviewed by two research assistants (NCR, AAK) who had been trained for this purpose, and supervised by three faculty members (SI, KJO, NHH) After excluding ineligible subjects (see inclusion and exclusion criteria below), patients were contacted

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telephonically. Permission for the interview was taken, and the subjects were then questioned a. about their initial symptoms to confirm that they were truly asymptomatic before the ultrasonography, and to determine if they had developed pain or any complications of gallstones (see complications below).

From the two private clinics, subjects who had come for executive health checks were identified from the databases. These subjects were typically healthy; nevertheless the records of these subjects were examined by five trained students from Universiti Teknologi MARA (PY, NY, HS, MHH, AF) and supervised by two senior consultants (AG, AAVA); then the subjects were called and interviewed.

The study was conducted over two years.

Inclusion and exclusion criteria

Patients were considered to have fulfilled the criteria of asymptomatic gallstones if a) the gallstones were discovered during an ultrasound study conducted for other reasons (e.g. executive check, pregnancy, check for renal stones), and b) if they had no pain in the right hypochondrium or in the epigastrium prior to the discovery of the gallstones. Bloating, indigestion, constipation, and diarrhoea were considered consistent with asymptomatic gallstones.¹⁶ A history of jaundice was not consistent with asymptomatic gallstones. Mindful of the fact that gall bladder colic can present as left sided abdominal pain, the surgeons (SS, NHH, KJ, HF) agreed that any such history would be an exclusion criterion if the pain was moderate or severe (>4 on a linear analogue scale). Also excluded were patients who had had the ultrasonography for upper abdominal pain, regardless of severity.

Complications

Patients were asked for complications after the discovery of the gallstones. Complications included a) significant pain (pain in the right hypochondrium or epigastrium regardless of severity, or pain in the left hypochondrium or epigastrium >4 on a linear analogue scale) and b) other complications, like acute cholecystitis, empyema, pancreatitis, or cancer.

Ethics approvals

The study was approved by the Ethics committee of Universiti Teknologi MARA (approval vide letter 600-RMI (5/16 dated 11 March 2010) and by the Medical Research and Ethics Committee, Malaysia (vide their letter (3) dlm. KKM/NIHSEC/08/0804/P12-122 dated 6 Aug 2012).

Statistical methods

The data were analysed using SPSS v.21 software. The demographic data were summarised for frequency and percent distribution. Kaplan-Meier survival analysis was used to summarise survival time. Log-rank tests and Kaplan-Meier curve were used to compare survival probabilities across gender, race and age. Cox proportionate hazard modelling was performed to estimate adjusted hazards and hazard ratios of gender, race and age.

To calculate sample size, we made the following assumptions: a) the rate of conversion is 2.5%/year,^{17,18} b) the rate of conversion is constant with time. Wanting an error of about

±1 at 95% confidence, the sample size *n* was calculated as follows:

$$n = 1.96^2(0.025*0.975)/0.01^2 = 936 \text{ subjects (followed up for a year, or equivalent)}$$

We therefore planned to achieve approximately 936 person-years of follow-up.

RESULTS

Several thousand subjects with gallstones were identified. From the crude records, 720 subjects fulfilled the criteria of asymptomatic gallstones. From among these, 213 were contactable, agreed to be interviewed, and, on interview, fulfilled the criteria for asymptomatic gallstones (Figure 1).

Participant characteristics

Of 213 participants, 112 (53%) were males. The majority were Chinese (50.7%) (Table I).

Table I: Participant characteristics

Characteristic	Number (%)
Gender	
Male	112 (52.6)
Female	101 (47.4)
Race	
Malay	84 (39.4)
Chinese	108 (50.7)
Indian	21 (9.9)

Conversion from asymptomatic to symptomatic

Of 213 subjects diagnosed to have asymptomatic gallstones, 23 subjects developed pain after a period of 1 to 54 months (females 1-54 months, males 2-41 months). This gives a gross conversion rate of 10.8%. No person reported jaundice or features suggestive of complications like pancreatitis, empyema, or cancer.

Time to conversion from asymptomatic to symptomatic

The follow-up period ranged from 28 to 4296 days (average 1467.6 days, 4.02 years). The participants were followed up from the date of entry (date of ultrasound diagnosis of gall stone) until the event (pain) or till the date on which they were contacted. The total follow-up period was 312,595 person-days (856.4247 person-years).

During these 4.02 years of follow up, 23 persons became symptomatic, giving a gross time-to-conversion of about 2.7 per cent per year. However, most conversions occurred within three years of follow-up (Table II).

Gender

Six of 112 males (5.36%) and 17 of 101 females (16.83%) converted from asymptomatic to symptomatic. A Cox proportional hazard regression analysis was performed to estimate adjusted hazard ratios for various factors which might affect the hazard of developing pain due to gall stones. Race and age had no significant contribution to the model, and gender turned out to be the only significant factor with a hazard ratio of 3.23 (±1.54 SE, 95% CI 1.27-8.20), indicating that females are over 3 times more likely to develop pain due to gall stones as compared to males.

Table II: Cumulative risks of developing pain

Year of follow up	Number starting the year without pain (N)	Number who developed pain this year	Cumulative risk of pain (%)*	Average % annual risk at years 2, 5 and 10 ± SE*
1st		213	10	4.88
2nd	185	6	8.06 (M 4.85, F 11.54)	4.03 ± 0.965 (M 2.42 ± 1.06 F 5.77 ± 1.64)
3rd	166	2	9.2	
4th	154	4	11.26	
5th	104	1	13.81 (M 6.15, F 22.1)	2.762 ± 0.578 (M 1.23 ± 0.49 F 4.42 ± 1.04)
6th	29	0	13.81	
7th	29	0	13.81	
8th	26	0	13.81	
9th	20	0	13.81	
10th	19	0	13.81 (M 6.15, F 22.1)	1.381 ± 0.289 (M 0.62 ± 0.25 F 2.21 ± 0.52)
11th	18	0	13.81	
Total		23	13.81	

*2 year, 5 year and 10 year averages and their respective standard errors were computed using data from lifetable analysis. The figures are for all cases, for males (M) and for females (F). N: Number at risk, excluding censored cases and those who developed pain in the previous year

Table III: Annual rate of development of complications (including symptoms) among patients with silent gallstones

Author	Diagnosis	Rate/year ± SE	No of subjects studied
Ross and Jayakumar, 1987 ²³	US ^a	0.1%	48
McSherry <i>et al</i> , 1985 ¹⁷	OCG ^b	2.15%	135
Del Favero <i>et al</i> , 1994 ¹³	US	3%	47
Attili <i>et al</i> , 1995 (1st two years) ¹⁸	US	5.95 ± 3%	118
Attili <i>et al</i> , 1995 (1st ten years) ¹⁸	US	2.6 ± 4.6%	118
Zubler <i>et al</i> , 1998 ⁸	US	7.3%	32
Present study (1st two years)	US	4.03 ± .097%	213
Present study (1st ten years)	US	1.38 ± 0.29%	213

^aUS: Diagnosis by ultrasonography, ^bOCG: Diagnosis by oral cholecystography

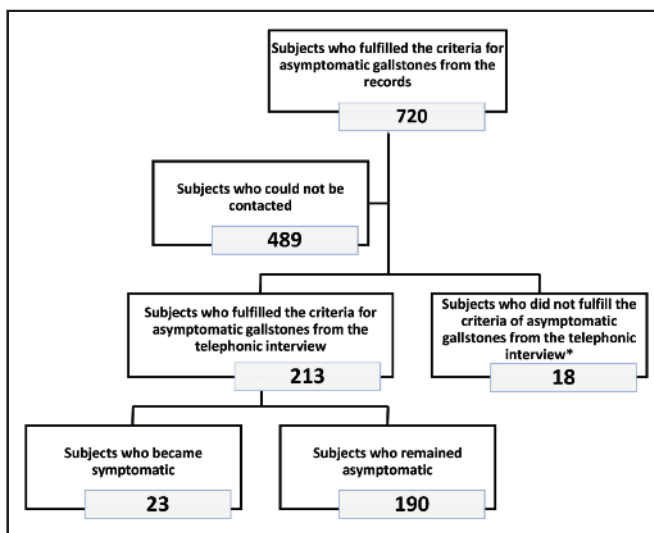


Fig. 1: Flow chart indicating the outcomes of the subjects who from the original records fulfilled the inclusion criteria for asymptomatic gallstones.

*One subject in this group declined consent for the interview.

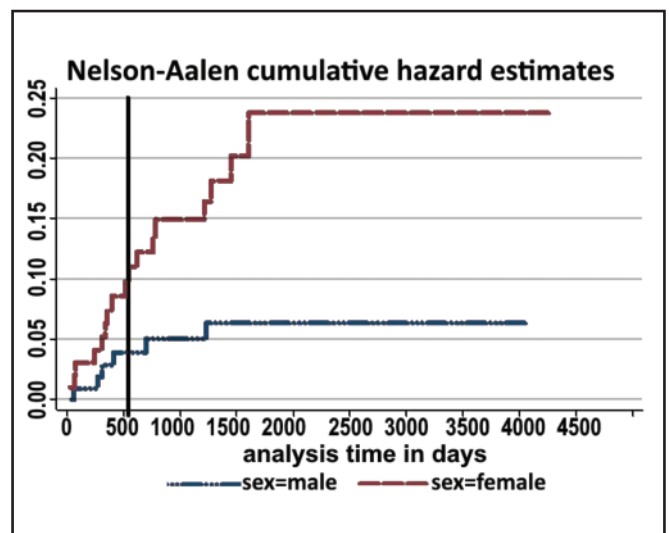


Fig. 2: Nelson-Aalen cumulative hazards by days and gender. The analysis time is measured in days after detection of the stones.

A Nelson-Aalen cumulative hazards curve shows that after 500 person-days of follow up, the hazard for developing pain becomes clearly greater in females when compared to males (Fig 2).

In years 1, 2, 3, 4 and 5 after discovery of the stone, 3, 2, 0, 1, and 0 males, and 7, 4, 2, 3 and 1 females converted from asymptomatic to symptomatic. No subject converted after five years.

Age and race

The age and race of subjects did not influence the likelihood of conversion.

DISCUSSION

Radiologists often discover silent gallstones during ultrasonography for other conditions (e.g. pregnancy). In recent years the "Preventive health check" has become popular. Companies often sponsor apparently healthy employees for screening,¹⁹ and may detect asymptomatic gallstones.

Surgeons are aware that asymptomatic gallstones do not always remain asymptomatic. Should these subjects undergo prophylactic cholecystectomy?

The surgeon's advice will depend on expert guidelines, which in turn will depend on the rate of conversion from asymptomatic to symptomatic gallstones. (The mortality of surgery is low, at about 0.1%, and does not become a serious factor in decision-making).²⁰ If the conversion rate is 2% per year, only half of all asymptomatic patients will develop pain in 35 years. Patients will not want surgery. If, however, the conversion rate is 7%, half of all asymptomatic patients will develop pain in ten years. Patients might prefer prophylactic cholecystectomy, lest they develop symptoms at an older age when mortality is higher.²¹

In published reports, the rates of conversion vary widely from 0.1% to 7.3% (Table III). There are at least two reasons for the wide disagreement in conversion rates. One is the fact that some earlier reports diagnosed gallstones using OCG,^{10,17} a test now known to be inaccurate.^{11,12,22} The second reason is that sampling errors are usually high, because of small sample sizes. For the error to be less than 1%, the sample size needs to approach 1200 person-years of follow up.

In the present study we look conversion rates in males and females. We also look at the data with respect to conversion rates over time.

Conversion rates

In our study, 23 of 213 (10.8%) subjects converted from asymptomatic to symptomatic over an average follow up of 4.02 years. Thus, one can expect a crude conversion rate of about 2.7% per year of follow up. This conversion rate is quite similar to that reported by Attili *et al.*¹⁸

However, conversion rates differed between males and females, and seemed to decrease over time.

Females were followed up for 4.19 years (median); during this time 17 subjects converted (approximately 4% per year). Males were followed up for 4.32 years; during this time 6

subjects converted (1.24% per year). If these conversion rates were to remain constant, about half of all males with asymptomatic gallstones would become symptomatic after 41-42 years, and females in 13-14 years.

Fortunately, conversion rates do not appear to decrease with time. After three years of follow up, only four subjects turned symptomatic of 154 starting out without symptoms. After four years, the figure was 1 of 104, and subsequently, none of 29 (16M, 13F) starting without symptoms developed any.

Given a lifetime risk of conversion of 6.15%, prophylactic cholecystectomy for males would seem to be hardly worthwhile. After 5 years of follow up the risk of developing pain could be considered to be negligible.

In contrast, in females the lifetime risk of conversion is 22%. The risks of symptoms are sufficiently high to seriously consider a surgical option. However, even in females, after five years of follow up the risks of conversion appear to be negligible.

For this reason, longer follow up durations more closely reflect the lifetime risks of developing pain. Gracie and Ransohoff⁰ reported the cumulated conversion rate at 10 years to be 15% for asymptomatic stones discovered on OCG. McSherry *et al.*¹⁷ followed up 135 persons with silent stones, and showed a 10% conversion rate after a follow up period that averaged almost four years. Our own data is similar: we find a 13.8% conversion rate at 10 years. In comparison, Attili *et al.*¹⁸ reported a somewhat higher cumulated probability of conversion: 25.8% at 10 years. It is difficult to explain the reason for this increased probability. Attili and co-workers themselves suggest a protopathic bias, indicating that the figure results might have been lower if the subjects had not known of the presence of the gallstones. Although their definition of biliary colic was quite specific, some subjects might have preferred cholecystectomy without having had true biliary colic.

The problem with concluding definitely that risks of conversion fall with time is that we really do not know when these asymptomatic stones developed. Nevertheless, there is a clear suggestion even in literature that as we move closer to the time of origin of the stone, the probability of symptoms is higher.^{10,18}

Prevalence of gallstones in men and women

Our data indicates that the probability of developing symptoms is three times higher for women than men. The GREPCO study²⁴ also observed that men seem to be less frequently symptomatic than women.

Why do gallstones become symptomatic in women far more commonly than in men? This is difficult to answer. Wang *et al.*²⁵ presented evidence that receptor-dependent effects of estradiol influence cholesterol supersaturation of bile.

Of course, this also raises the question of whether gallstones are actually commoner among women, or do they simply present more often? This discussion is beyond the scope of this study, but conflicting information has been raised in the literature.^{24,26-29,30,31}

Interestingly, the average age of discovery in our study (58 years) is almost identical to that reported by Zubler *et al*,⁸ and is consistent with the finding that gallstones tend to occur in the sixth and seventh decades.^{4,30}

Strength and limitations of the current study

To our knowledge this is the first time that a retrospective cohort study has been planned to study the natural history of gallstones. This design has some advantages. It allows the collection of larger numbers of subjects for study, and for long follow up. This reduces the sampling error: our numbers were large enough to lower the standard error below 1. Finally, a retrospective study largely avoids the protopathic effect described for prospective studies¹⁸ – that subjects may start to be excessively aware of or imagine pain once they know that they have gallstones.

There are obvious limitations, however. The retrospective design of the study introduces the possibility of a recall bias. We presume that this will be small, since the average follow up was 4 years, and a painful event like biliary pain is one not easily forgotten. Nevertheless, it remains a concern that should be addressed if further studies are planned. With this design it is impossible to decide the prevalence of the disease. Although we found more asymptomatic males than females, this could simply be because males might be more likely to come to hospitals and to come for preventive health checks.

Although the telephonic interview is a well-established method for gathering data^{13,18} it is still naturally weaker than the face-to-face interview. Finally, our subject selection was not random. Our data source was not randomised. Instead, we chose the only hospital within 50 km that had electronic records: extracting data from other hospitals proved to be impossible. Private clinics, in contrast, do maintain electronic records, but our choice was dictated from a personal affiliation to the radiologists in these clinics.

In conclusion, we believe that our data indicates that asymptomatic gallstones convert to symptomatic much less frequently in males than in females. Males with asymptomatic stones could generally be offered non-operative treatment. For females the picture is different. If one knows that the stone has been present for over five years, the probability of developing pain is negligible. What if a young female has an asymptomatic stone that has just been detected? In that case, given that the lifetime risk is over 20%, and given the safety and low morbidity of surgery today, a surgeon would probably do well to advise intervention.

List of Abbreviations

OCG: Oral cholecystography
US: Ultrasonography

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