The clinical value of abdominal symptoms and sonography in gallstone disease

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The clinical value of abdominal symptoms and sonography in gallstone disease

Klinische waarde van buikklachten en echografie bij galstenen

Proefschrift

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- J.J. van der Velden, M.Y. Berger, H. Pala, K. Brakel, H.J. Bonjer, J.S. Lameris. Can sonography predict conversion of laparoscopic to open cholecystectomy? A prospective study. *Submitted for publication*
- J.J. van der Velden, M.Y. Berger, H.J. Bonjer, K. Brakel, J.S. Laméris. Can sonographic signs predict long-term results of laparoscopic cholecystectomy? *Hepatogastroenterol 1999; 46:3063-7*
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Voor Marlon, Matthijs en Roel

ntroduction

Gallstones are a very common finding in adults of Western industrialised countries. At age 60 almost 30% of women and 20% of men will have developed gallstones (Fig. 1[1-6]). Gallstones are rare in children. The prevalence of gallstones is most probably equal between the sexes until puberty, whereafter prevalence increases faster with increasing age among women than men. Gallstones occur more among women than among men at almost every age. After the menopause, the increase seems fairly equal in the two sexes with a marked narrowing of the gender gap with advancing age[7].

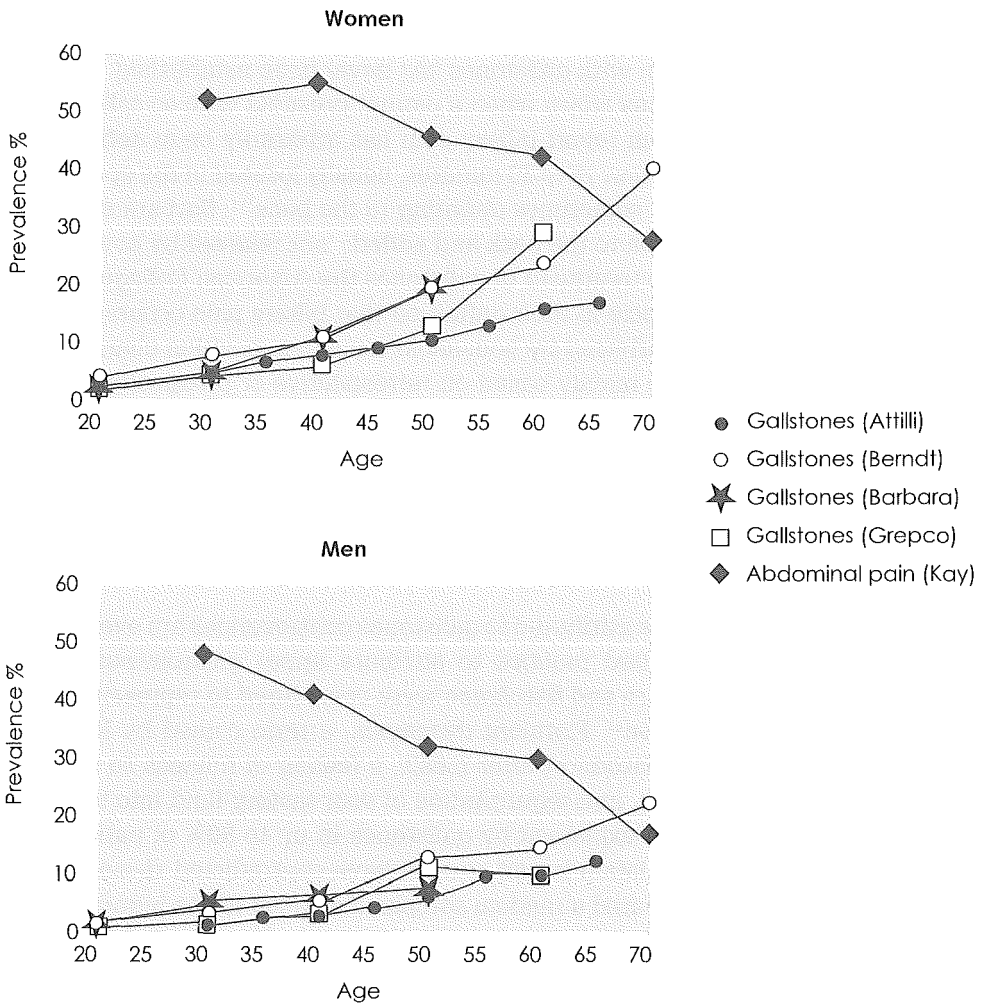

Figure 1

Asymptomatic and symptomatic gallstones

Most gallstones are asymptomatic; 80% of the subjects with gallstones is free of symptoms[1-3]. These so-called silent gallstones appear to carry a low risk of developing symptoms with time[8]. Prophylactic cholecystectomy for silent gallstones was shown to cause a decrease in survival and to incur more costs when compared with expectant management. Therefore consensus exists that silent gallstones in patients without co-morbidity should not be surgically treated[9,10].

In a person with symptomatic gallstones symptoms tend to persist or recurr. Without intervention biliary complications occur at a rate of 1% to 2% per year[10]. Prophylactic cholecystectomy is recommended for most patients with symptomatic gallstones[10].

The term 'symptomatic gallstones' is widely used and implies that it is known what symptoms gallstones specifically cause. A whole range of symptoms has been attributed to gallstones, but a causal relation with gallstones has never been established.

A clinical suspicion of gallstones arises when a patient presents with so called biliary pain. In the Roma88 working team report biliary pain has arbitrarily been defined as 'a severe steady pain, lasting more than 15 to 30 minutes, usually located in the epigastrium and/or right upper quadrant, and sometimes radiating to the back'[11]. Barbara et al[1] used the definition without the radiation to the back and added: 'not relieved by bowel movements'. In their guidelines for the treatment of gallstones the American College of Physicians followed Ransohoff and Gracie in their definition that biliary pain occurs suddenly as severe steady pain that is unaffected by household remedies, position change or gas passage[9,12]. These definitions are mainly based on retrospective or prospective descriptions of abdominal symptoms in patients with gallstones without the use of a control group. Prevalence studies comparing the presence of abdominal symptoms between patients with gallstones and those without, found contradicting results about the association between biliary pain and gallstones. Barbara et al[1] found a significant relation between their definition of biliary pain and gallstones, but Jørgensen et al[13] could not confirm this association.

For other abdominal symptoms attributed to gallstones controversies are even greater. Early last century, it was standard practice to attribute upper gastrointestinal tract symptoms to gallstones. Heartburn and flatulence were considered to represent inaugural symptoms of gallstone disease[14]. Flatulent dyspepsia, a term coined by Rhind and Watson[15] to refer to epigastric discomfort after meals, a feeling of fullness so that tight clothing was loosened, eructation, and regurgitation of sour tasting fluid into the mouth with heartburn, was found to be explained by gallstones in up to 80% of patients who sought medical care. Later population based studies have contradicted these findings. For example, Bainton et al[16] evaluated a random sample in a South Wales industrial town and found that the symptoms of dyspepsia occurred with an approximately equal frequency in those with and without gallstone disease.

Besides preventing gallstone complications like acute cholecystitis, one must logically

assume that cholecystectomy would relieve symptoms that were due to gallstones. So if surgery is performed in patients with symptomatic gallstones, what is the outcome? Several studies have reported that 45-80% of patients with gallstones and dyspepsia obtained partial or complete relief of symptoms following cholecystectomy[17,18]. Dyspeptic symptoms, however, have the prospect of disappearing spontaneously. In two population based studies dyspeptic symptoms disappeared within one year in 15-35%[19,20]. In a study of patients visiting their general practitioner with abdominal pain 69% of patients were symptomfree after one year[21]. The placebo response in functional dyspepsia - that is dyspepsia without a structural or biochemical explanation - approached 70%[22].

In patients with gallstones operated for biliary pain 73-94% obtained relief of their symptoms after cholecystectomy[23,24]. Unfortunately studies evaluating post-operative relief of biliary pain either did not use a control group or did not follow the controls over time.

The assumption has often been that if gallstones are found in symptomatic cases then gallstones are the cause of the symptoms and referral for cholecystectomy is indicated. But whereas both gallstones and abdominal symptoms, including pain, are common in adults[6], the occurrence of both might be due to chance alone.

Ultrasonography is an accepted procedure to establish the presence of gallstones in the gallbladder. It is fast, it is convenient, there is no radiation risk, the reliability of the method is high and it is widely available for a broad range of physicians including general practitioners[7]. Reluctance to use ultrasonography in patients with vague abdominal symptoms is therefore diminished to a minimum. This will further increase the probability of a chance finding of gallstones in patients with abdominal symptoms.

The popularity of laparoscopic cholecystectomy has made the choice for direct surgical treatment even more attractive. Laparoscopic cholecystectomy has become the treatment of first choice since the early nineties[25]. It is a less expensive and safer procedure than open cholecystectomy and can be performed on an outpatient basis[26].

Since the introduction of this procedure the number of cholecytectomies has increased, with estimates of the increase varying from 20-60%[27,28]. This increased cholecystectomy rate may reflect increased patient acceptability, particular in the older patients, but may as well reflect a lowered surgical treshold[29]. Despite evidence that the age specific prevalence rate of both symptomatic and asymptomatic gallstones is much the same in North America and in England and Wales, cholecystectomy rates in North America are 3-4 times higher compared to those in England. This implies that the indication for cholecystectomy is to some degree arbitrary, and unnecessary interventions will occur[30].

Recommending all patients with symptomatic gallstones to receive surgery is an empty recommendation as long as the most difficult question can not be answered: who is symptomatic?

Few studies have evaluated whether the radiographic appearance of gallstones predisposes them to cause symptoms. In a consecutive series of 260 patients with newly diagnosed, uncomplicated gallstone disease, Ros et al[31] used ultrasonography and oral

cholecystography to find that a non-visualised gallbladder, multiple stones, and those that were small or of dissimilar size were associated with biliary pain. In their population study GREPCO[32] could not confirm these findings. An important question remains whether radiological characteristics of gallstones and gallbladder can predict the symptomatic outcome after cholecystectomy.

Aims of this thesis

The aim of this thesis was to identify the symptoms that are most closely associated with gallstone disease in order to evaluate whether these symptoms are able to predict the clinical outcome after cholecystectomy. In addition we aimed to evaluate the prognostic value of sonographic findings for the clinical outcome after cholecystectomy.

In *chapter 1* the results of a systematic review of studies evaluating the diagnostic accuracy of abdominal symptoms for the radiographic presence of gallstones are presented.

Chapter 2 focuses on the diagnostic accuracy of a combination of abdominal symptoms for gallstones, using data from a prospective study of patients presenting at their general practitioner with symptoms suggestive of gallstones.

Chapter 3 presents a literature review of studies evaluating the prognostic value of separate pre-operative symptoms on the outcome of cholecystectomy.

In *Chapter 4* the results of a prospective study evaluating the association between pre-operative sonographic findings and symptom relief after elective laparoscopic cholecystectomy are presented.

Chapter 5 evaluates the additional prognostic value of pre-operative sonographic findings above the prognostic value of a combination of pre-operative abdominal symptoms for the outcome after cholecystectomy.

In *Chapter 6* a decision analysis comparing two treatment options – expectant management versus laparoscopic cholecystectomy in patients with abdominal symptoms and gallstones – is used to evaluate the clinical relevance of the findings of this thesis.

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1 Abdominal symptoms: do they predict gallstones?

A systematic review

Abstract

BACKGROUND: *our objective was to evaluate the diagnostic accuracy of abdominal symptoms in gallstones in studies using ultrasonography or oral cholecystography as the ref-erence standard and to assess the extent to which variability in diagnostic accuracy is explained by patient selection, and other characteristics of study design.*

METHODS: *A Medline search (1966-1998) was conducted in combination with ref-erence checking for further relevant publications. Two independent assessors selected controlled studies that included patients ≥18 years of age. Articles were excluded if sensitivity and specificity could not be extracted, or the included patients were at extraordinary risk for gallstones. Seven abdominal symptoms were evaluated. Modification of the diagnostic accuracy by clinical setting, extent of the disease, blinding, age and sex was analysed by using logistic regression.*

RESULTS: *A total of 24 publications were included. The symptoms "biliary colic", "radiating pain" and "analgesics used" were consistently related to gallstones. The setting of the study had a significant effect on the diagnostic accuracy of these symptoms. The unadjusted, pooled diagnostic odds ratios, however, were low (2.6 (95% confidence interval 2.4-2.9), 2.8 (2.2-3.7) and 2 (1.6-2.5) respectively). The diagnostic odds ratio of biliary colic increased with the extent of gallstone disease (13.3 (4.2-42).*

CONCLUSIONS: *Although biliary colic was specific for gallstones, 80% of the referred patients with gallstones presented with other abdominal symptoms. There is no current evidence that justifies the use of single abdominal symptoms, other than biliary colic, in the diagnosis of symptomatic gallstones. Further research should focus on the prognosis of patients with non-specific abdominal symptoms and gallstones.*

Gallstones occur frequently in the adult population, and by the age of 60 about 30% of women and 20% of men have developed gallstones[1-3]. most persons with gallstones are asymptomatic, but in some, gallstones cause abdominal pain, acute biliary complications and gallbladder cancer. There is general agreement that symptomatic gallstones should be treated[1]. The diagnosis of the presence of gallstones is relatively easy to assess by ultrasound. In contrast, determination of whether a patient's symptoms can be attributed to gallstones represents an important diagnostic challenge for primary care physicians. The diagnosis of symptomatic gallstones is based primarily on medical history. To define the symptom status of a patient with gallstones, it is important to know which symptoms are related to gallstones. Knowledge about the symptoms that occur more in patients with gallstones than in those without is a first step in elucidating this question.

Studies on the discriminative capacity of abdominal symptoms for gallstones have produced widely varying results[4]. A Danish screening study was unable to define any abdominal symptom or combination of symptoms as specific for gallstones[3], whereas a study based on referred emergency cases found significantly more attacks of acute abdominal pain and intolerance to fatty foods in patients with gallstones[5]. Meta-analysis is valuable in assessing the accuracy of diagnostic tests[6]. Summarising these heterogeneous results into a simple estimate of diagnostic accuracy can, however, be misleading because clinically important discrepancies are ignored[7].

We therefore systematically reviewed the evidence with regard to the ability of various abdominal symptoms to diagnose gallstones. We considered the effect of differences in patient selection, clinical setting, and study design on the diagnostic accuracy of these symptoms.

Materials and methods

A systematic literature search was conducted in Medline (January 1966 to May 1998) of all English-, French-, Dutch- and German-language articles investigating the diagnostic accuracy of abdominal symptoms in gallstones in humans. Combinations of the search keys "cholelithiasis" and "abdominal pain" as MeSH headings were used with "symptom", "sign" and "complaint" as (part of) text words. Additional references were obtained from the bibliographies of review articles and original papers. Articles were excluded from further consideration if they met one of the exclusion criteria listed in Table 1. Two independent readers (M.Y. Berger and H. de Kort) reviewed the abstracts of all publications, blinded for the source and authors of the publication. Consensus was reached in cases of disagreement.

Blinding

The reader of the reference standard had to be unaware of the symptoms of the patient. If independent reading of the reference standard was not described, we assumed no independence.

Table 1
Exclusion Criteria

1. No original data used.
2. Reference standard other than ultrasound or oral cholecystography.
3. Study group restricted to patients under 18 years of age.
4. Patients living in non-comparable circumstances (e.g. Pima Indians) or patients with extreme conditions selected as study group (e.g. only patients with diabetes mellitus).
5. True positive rate and false positive rate were not reported and could not be calculated from the data presented.

To evaluate the methodological quality of the included studies a standard form was used to extract pertinent data from these articles (Table 2).

Setting

All studies were divided into two groups: 1) studies based in the general population in which a (random) sample of the population was invited for gallstone screening, and 2) hospital-based studies in which patients were referred for gallbladder investigation because of abdominal symptoms.

Spectrum of the disease

In all hospital-based studies in which patients with abdominal symptoms were referred we evaluated the spectrum of the disease. The definition "mild disease" was applied when the patients were so described and in all studies in which referral was elective. The definition "serious disease" was applied when the patients were so described, and in all studies with emergency referrals or hospitalized patients. The definition "no disease" was applied to all studies based in the general population.

Patient characteristics

Sex and age are factors known to be related to the presence of both symptoms and gallstones. These factors may influence the association between symptoms and gallstones.

The symptoms and signs evaluated are (upper) abdominal pain, biliary colic, radiation of the pain to the back or shoulder, use of analgesics to ease the pain, tenderness of the upper right quadrant of the abdomen, food intolerance, and fat intolerance.

Analysis

In the estimates of the prevalence of gallstones only persons with intact gallbladders were included. Persons with a history of cholecystectomy were excluded. For each study the true positive rate (= sensitivity) and the false positive rate (= 1-specificity) were

calculated from the published data. Subsequently, the estimates of the true positive rate were plotted against the estimates of the false positive rate. In these plots outliers could be identified. Tests for homogeneity by means of the chi-square statistic were performed seperately for true positive rates and false positive rates. In case of heterogeneity ($P>0.05$) a logistic regression model with the probability of a symptom being present as the dependent variable and disease status as an independent variable was used to evaluate whether 1) setting, 2) spectrum of the disease, 3) sex of the study population, 4) blinding of the radiologist, and 5) the reference standard significantly influenced the discriminative capacity of the abdominal symptoms ($P<0.05$). The models with one of these variables added, were compared with a model without the variable, using generalized likelihood ratios test statistics[8]. All characteristics of the study design were evaluated separately, as the small number of studies evaluating one, single abdominal symptom precluded performing a multivariable analysis. Logistic regression was used to estimate a pooled diagnostic odds ratio. The diagnostic odds ratio is a function of the true positive rate and the false positive rate and is a measure of diagnostic accuracy:

$$\text{Diagnostic odds ratio} = \frac{(\text{true positive rate}/(1-\text{true positive rate}))}{(\text{false positive rate}/(1-\text{false positive rate}))}$$

A diagnostic odds ratio of 1.0 indicates no discriminative capacity. The diagnostic odds ratio is >1.0 if the symptom occurs more often in subjects with gallstones than without, and it is <1.0 if the reverse is true. In the present study we assumed the diagnostic odds ratio to be independent of the threshold used. Asymptotic 95% confidence intervals around the diagnostic odds ratio were calculated. All computations were performed with SPSS for Windows software, version 6.1[9].

Results

From a total of 329 publications, 311 were excluded. Six additional publications were found in the reference lists and were included in the analysis[15,18,24,27-29]. Thus, 24 studies could be analysed (Table 2).

Only Wegge & Kjaergaard[5] used the clinical course as a reference in adition to ultrasonography. In 16 studies no blinding procedure for the reader was described. Fourteen studies were based in the general population and 10 studies were hospital-based. Of the hospital-based studies four studies selected patients with "mild disease", and six studies selected patients with "serious disease". In eight studies[3,11,19-21,24-26], either restriction or stratification by sex and age was used to control for confounding. Four studies controlled for sex either by stratification[2,16,17] or restriction[27], but used a wide age range. In all other studies there was no control for confounding by these factors.

A total of 36,302 patients was studied; 4891 (13.5%) of these patients had gallstones. The prevalence of gallstones depended on the setting of the study; in the general population the prevalence was 12.4% (3967 of 31,993); in a referred population the prevalence

Table 2
Publications included in the analysis.

Author (ref)	Patient selection	Extent of disease	Men (n)	Women (n)	Age (Years)	Blinding of radiologist	Reference standard	Prevalence of gallstones % (n)
Screening studies in the general population								
Attilli (2)	Random sample general population		15433	12617	30-69	Yes	US	9 (2480)
Jørgensen (3)	Random sample national register		1719	1598	30-60	No	US	6 (207)
Barbara (10)	Subjects registered in the Municipal Census		859	974	18-65	Yes	US	7 (132)
Bainton (11)	Random sample from electoral roll		700	0	45-69	Yes	OC	5 (34)
Berndt (12)	Selected sample of general population		661	1030	14-75	No	US	22 (377)
Glambek (16)	Random sample general population		632	697	20-70	No	US	22 (285)
Heaton (17)	Patients registered with 19 general practices		824	1021	25-69	No	US	5 (92)
Janzon (19)	Participants in a health survey		0	383	48 & 53	No	Both	11 (43)
Mellström (21)	Participants in a health survey		0	83	77-78	No	US	35 (29)
Price (24)	Patients registered with one general practice		0	142	50-70	No	OC	17 (24)
Grepco (25)	Women on payroll of government department		0	1045	20-64	Yes	Both	6 (66)
Grepco (26)	Men on payroll of government department		1202	0	20-69	Yes	Both	5 (65)
Wilbur (27)	Participants in a health survey		1208	0	35-55	No	OC	8 (92)
Muhrbeck (30)	Random sample general population		250	265	40 & 60	Yes	US	8 (41)

Hospital-based studies involving referred patients								
Wegge (5)	Emergency cases with upper abdominal pain less than one week in duration referred to a teaching hospital	Serious	70	122	-	No	US+OC+ follow-up	26 (49)
Diehl (13)	Patients suspected for gallstones, referred to the emergency room and the walk-in clinic of a teaching hospital	Serious	48	252	-	No	Both	41 (122)
Farrell (14)	Patients suspected for gallbladder stones referred to a radiology department by their general practitioner (44.6%), outpatient department (21%) or inpatients (34.4%)	Serious	87	213	39+	No	Both	33 (98)
Galatola (15)	Consecutive patients with abdominal pain attending a gastroenterology outpatient clinic	Serious	153	129	17-89	No	US	15 (41)
Hinkel (18)	Patients with abdominal symptoms referred to a radiology department	Mild	332	668	10-70	No	OC	17 (173)
Massarrat (20)	Patients without abdominal pain referred to a radiology department	Mild	65	97	50+	No	OC	25 (41)
Mills (22)	Patients referred for abdominal US by their general practitioner or the outpatient department	Mild	-	-	19-29	No	US	15 (87)
Peter (23)	Patients referred for abdominal US	Mild	-	-	20-90	Yes	US	19 (256)
Paul (28)	Patients referred for cholecystectomy and healthy controls	Serious	96	25	21-80	No	Both	
Koch (29)	Hospitalized patients referred for OC	Serious	-	-	-	Yes	OC	44 (57)

- = not specified
US = ultrasonography
OC = oral cholecystography

Table 3
Prevalence of gallstones, the frequency of the symptom being present, the predictive value of a positive test and the predictive value of a negative test, in accordance with the setting of the study, in percentages

	General population				Referred population			
	Prevalence of gallstones (number of patients)	Frequency of symptom	Predictive value positive test	Predictive value negative test	Prevalence of gallstones (number of patients)	Frequency of symptom	Predictive value positive test	Predictive value negative test
Upper abdominal pain	12 (8890)	14	23	90	29(2056)*	60	30	79
Biliary colic	8 (34649)	7	17	92	22 (1305)	9	50	81
Radiating pain	8 (515)	19	10	93	28 (1224)	45	38	81
Use of analgesics	14 (2936)	23	24	89	26 (192)	61	50	81
Tenderness upper abdomen	-	-	-	-	34 (792)	52	40	73
Food intolerance	9 (1617)	25	9	92	20 (2402)	45	23	82
Fat intolerance	14 (2835)	11	16	86	24 (2746)*	35	30	79

* Paul et al.[28] excluded

was 21% (924 of 4309). In both settings, the prevalence of gallstones varied widely (5-35% and 11-50%, respectively). Except for "biliary colic", the frequency of the symptom being present, doubled in the referred patients compared with the general population. The risk of having gallstones, given an abdominal symptom being present, never exceeded 50% (Table 3). The unadjusted pooled diagnostic odds ratio of all symptoms studied was low (Table 4). True positive rates and false positive rates are plotted in Fig. 1. True positive rates and false positive rates are found on or a little above the diagonal axis for the symptoms abdominal pain and biliary colic (Fig. 1a and b), suggesting that the symptoms occur only slightly more in patients with gallstones than in those without. For the symptoms food and fat intolerance the true positive rates and false positive rates are spread around the diagonal axis, suggesting that food and fat intolerance occur as often in patients with gallstones as in those without (Fig. 1c and d). The chi-square test statistic showed heterogeneity of both the true positive rates and false positive rates of all symptoms studied ($P<0.001$). For the symptoms abdominal pain, biliary colic, and the use of analgesics logistic regression showed a significantly different diagnostic accuracy for different clinical settings (Table 4). The setting of the study also had an effect on the discriminative capacity of radiating pain, but this did not reach statistical significance. Different spectra of disease showed a significantly different discriminative capacity in the symptoms abdominal pain, biliary colic and food intolerance.

Neither the sex of the studied population nor blinding of the reader to the reference standard, nor the reference standard used could explain the heterogeneity in the results. Lack of control for confounding by age in most studies precluded the evaluation of age as an explanation for the discrepancies in the results.

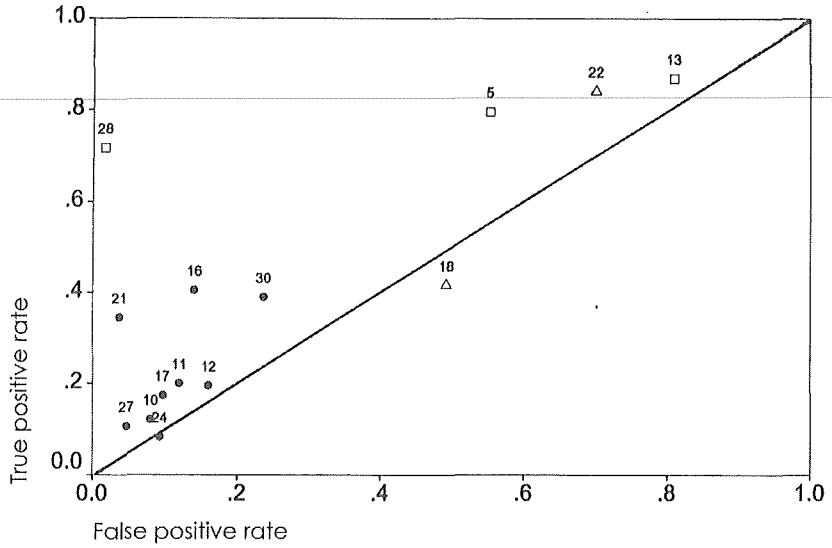
Abdominal pain (Fig. 1a)

One outlier[28] was identified. In this study patients referred for cholecystectomy were compared with healthy controls. These controls will be less likely to have abdominal symptoms, thus creating an underestimation of the false positive rate; this study was excluded from further analysis. In referred patients with mild disease abdominal pain was found less frequently in patients with gallstones (Table 4). This finding was due to the inclusion of the results of the study of Hinkel & Moller[18], in which upper abdominal pain was found to exclude gallstones (diagnostic odds ratio 0.84 (0.65-1.1). In this study, involving referred patients with mild disease, the unblinded radiologist interviewed the patient before oral cystography and asked for "non-specific right upper quadrant pain" and "biliary colic". This procedure might have lead to a diagnostic odds ratio<1.0 for non-specific right upper quadrant pain. After exclusion of the latter study, setting, spectrum, and reference standard used had no statistically significant effect on the discriminative capacity of abdominal pain.

Biliary colic (Fig. 1b)

Biliary colic was defined in six studies[1,10,15,25,26,30] as "a steady right upper quadrant abdom-

a. Abdominal pain



b. Biliary colic

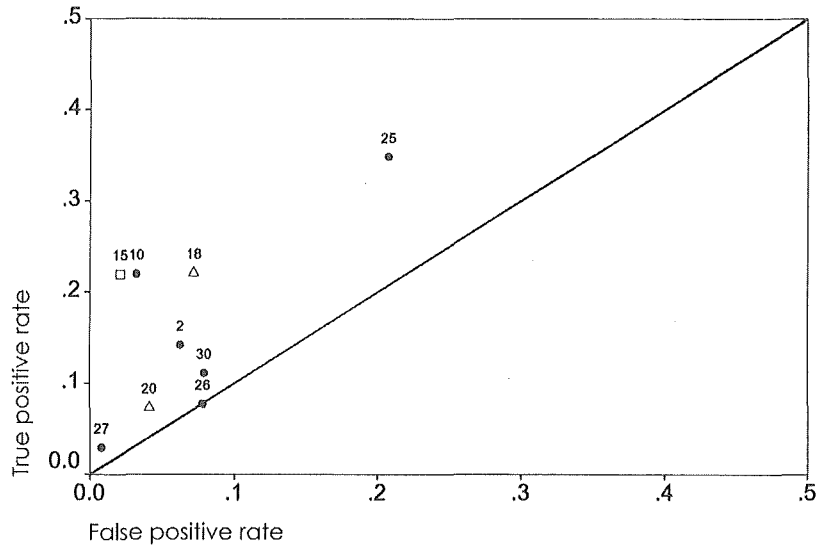
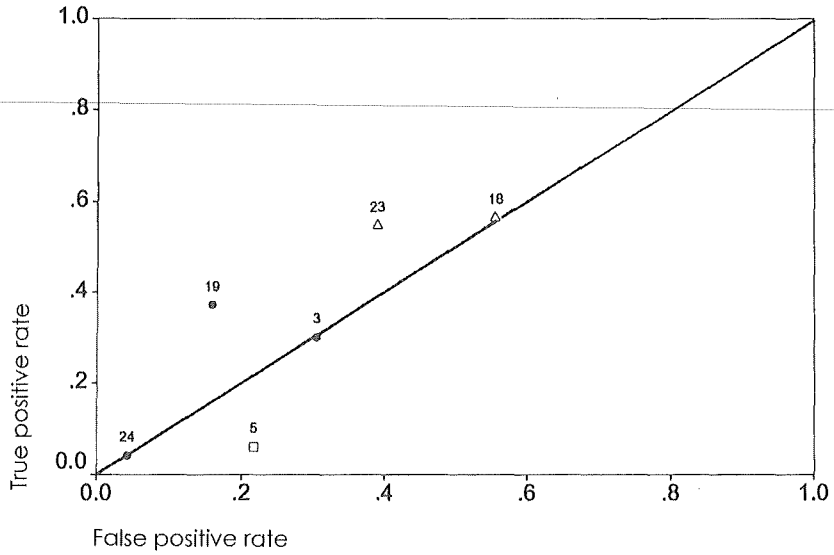


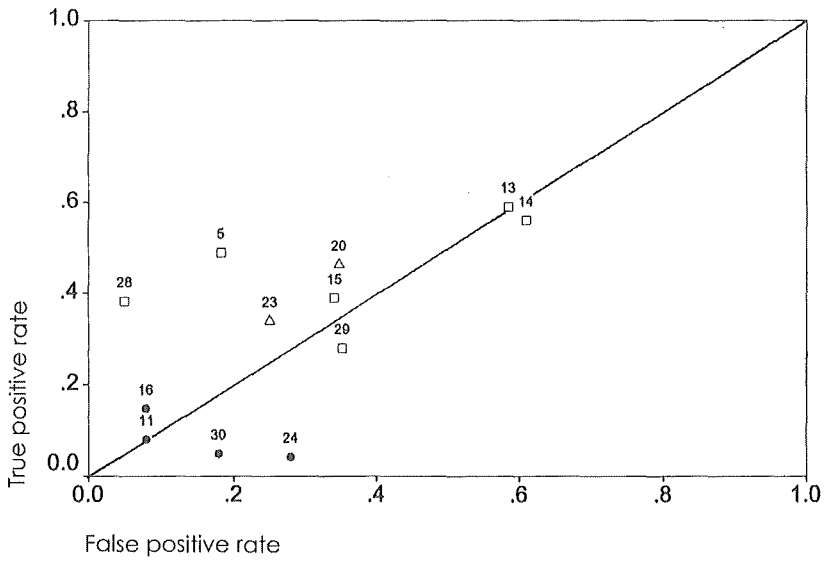
Figure 1

Plot of true and false positive rates for upper abdominal pain **(a)**, biliary colic **(b)**, food intolerance **(c)** and fat intolerance **(d)**. Each symbol represents the estimates of the true and false positive rates of one article. Reference numbers are printed above the symbols.

c. Food intolerance



d. Fat intolerance



● = general population, no disease
△ = referred patients wild mild disease
□ = referred patients with serious disease

inal pain lasting for more than half an hour", either with "radiation to the back and associated with nausea"[15] or "not relieved by bowel movements"[10] or "forcing the subject to stop what he is doing"[30], and in three studies[18,20,27] simply as "biliary colic". The findings indicate that biliary colic occurs more often in women (22%)[25] than in men (6%)[26,27], but the discriminative capacity is comparable for the sexes. In one study of referred patients with serious disease biliary colic distinguished best between patients with and without gallstones (Table 4). However, the estimates of this latter study were comparable to those of the study of Barbara et al.[10], which was based in the general population.

Food intolerance (Fig. 1c)

The difference in the discriminative capacity of food intolerance with regard to the disease spectrum was due to one study by Wegge & Kjaergaard[5] involving referred patients with serious disease (Table 4). In their study food intolerance occurred more often in patients without gallstones; this study was the only one that explicitly excluded intolerance for fatty or smoked food from the definition of "food intolerance".

Fat intolerance (Fig. 1d)

There were two outliers[24,28]. As mentioned above, the study of Paul et al.[28] was flawed by bias and excluded from further analysis. The other study[24] included women aged 50-70 years only. In this latter study gallstones were less prevalent in women with fat intolerance (diagnostic odds ratio 0.11 (0.01-0.86)). Four of the 24 women with gallstones, however, avoided fat on medical advice, but had previously noticed fat intolerance. Taking this into account, the results of this study were no longer significantly different from the results of other studies (diagnostic odds ratio 0.67 (0.23-2.0)) (Table 4).

Discussion

Seven abdominal symptoms suggestive of gallstones were evaluated in a meta-analysis of 24 studies on the diagnostic accuracy of abdominal symptoms for gallstones. The methodological quality of most included studies was low. Only eight studies blinded the reader of the reference standard to the abdominal symptoms of the patients, only eight studies controlled for both age and gender, and in the hospital-based studies the extent of gallstone disease in the included patients was barely described. This lack of methodologic quality, however, could not explain the heterogeneity of the reported diagnostic accuracy of the abdominal symptoms.

The symptoms biliary colic defined as "a steady right upper quadrant abdominal pain lasting for more than half an hour", "radiating pain" and "analgesics used" were the only three symptoms consistently related to gallstones, although their unadjusted estimates of diagnostic accuracy remained low.

These three symptoms had a better diagnostic accuracy in referred patients, although

Table 4
Pooled diagnostic odds ratios, unadjusted and adjusted for characteristics of study design

Symptom	Unadjusted	Setting		Spectrum		Blinding		Reference standard		
		General population	Referred population	Mild disease	Serious disease	Yes	No	Ultrasound	Oral cholecyst-ography	Both
Upper abdominal pain	1.7 (1.5-2.0) n=13	2.3 (2.0-2.7) n=9	1.1 (0.9-1.3)* n=4	0.9 (0.7-1.2) n=2	2.1 (1.3-3.5)* n=2	1.7 (1.2-2.4) n=4	1.8 (1.6-2) n=9	2.1 (1.3-3.5) n=6	0.9 (0.7-1.1)* n=4	2.4 (2-2.8) n=3
Biliary colic	2.6 (2.4-2.9) n=9	2.6 (2.3-2.9) n=6	4.1 (2.8-6.1)* n=3	3.5 (2.3-5.3) n=2	13.3 (4.2-42) n=1	3 (2.2-4.1) n=5	2.6 (2.3-2.9) n=4	2.7 (2.4-3) n=4	3.5 (2.3-5.2) n=3	1.7 (1.1-2.6) n=2
Radiating pain	2.8 (2.2-3.7) n=5	1.5 (0.7-3.1) n=1	2.7 (2.1-3.7) n=4	-	-	-	-	1.6 (0.9-2.7) n=2	-	2.6 (1.9-3.5) n=3
Use of analgesics	2 (1.6-2.5) n=4	1.8 (1.4-2.2) n=3	4.1 (2.8-6.1)* n=1	-	-	1.7 (0.6-4.6) n=1	2 (1.6-2.5) n=3	-	-	-
Tenderness upper abdomen	1.8 (1.3-2.4) n=3	-	-	-	-	-	-	-	-	-
Food intolerance	1.3 (1.1-1.6) n=6	1.4 (1-2.2) n=3	1.3 (1.1-1.6) n=3	1.4 (1.2-1.8) n=2	0.2 (0.1-0.8)* n=1	1.9 (1.4-2.5) n=1	1.1 (0.8-1.4) n=5	1.6 (1.3-2.1) n=2	1 (0.8-1.4) n=2	1.2 (0.7-2.2) n=2
Fat intolerance	1.3 (1.1-1.5) n=11	1.2 (0.9-1.7) n=4	1.3 (1.1-1.6) n=7	1.6 (1.2-2.0) n=2	1.2 (0.9-1.7) n=5	1.2 (1-1.5) n=4	1.5 (1.2-1.9) n=7	1.5 (1.2-1.9) n=4	0.9 (0.6-1.4) n=4	1.2 (0.9-1.7) n=3

( ) 95% confidence intervals in parentheses,
n number of publications
* Differed significantly from other categories P<0.05.
\- Diagnostic odds ratio could not be calculated due to lack of control.

this difference did not reach statistical significance for radiating pain; which might be explained by the small number of studies included in the analysis of this symptom. The diagnostic accuracy of biliary colic further increased with the extent of the disease. This finding was based on the results of one single study by Galatola et al.[15], involving seriously ill, referred patients. Seriously ill patients are more likely to be referred; thus part of the difference in diagnostic accuracy between the general population and a referred population is explained by the effect of severity and extent of gallstonedisease on diagnostic accuray[31]. However the small number of studies evaluating these symptoms precluded performing a multivariable analysis.

The discriminative capacity of upper abdominal pain was not better in referred patients. This might be explained by the presence of referral bias; only those patients without abdominal pain who had other (unknown) symptoms suggestive of gallstones were referred[6,32]. In this case the diagnostic accuracy will be underestimated (Fig. 1a).

In the present analysis fat intolerance and food intolerance were of very little value in diagnosing the presence of gallstones. This is in contrast to the findings of a meta-analysis by Kraag et al.[4], who found a pooled diagnostic odds ratio for food intolerance of 9.0 (6.2-13.0). However, one outlier[23] dominated this pooled diagnostic odds ratio. In our analysis we could not reconstruct their results for this particular study.

Recommendations for practice and future research

To prevent cholecystectomy for an innocent condition such as asymptomatic gallstones, one needs to know the specific symptoms of gallstone disease. Biliary colic, described as "an episodic, severe steady pain, lasting more than 15 minutes", is said to be such a symptom[1]. Although the present analysis affirmed this relation the discriminative capacity of biliary colic was low. Biliary colic occurred in 20% of the patients with gallstones and 6% of the patients without gallstones. In total, 80% of the patients with gallstones were referred with other abdominal symptoms. The discussion remains whether these latter patients had asymptomatic gallstones or their gallstones caused symptoms other than biliary colic. Primary care physicians may decide that a patient with biliary colic and gallstones has "symptomatic gallstones" and should be treated; with regard to simple upper abdominal pain or radiating pain, this diagnosis remains uncertain and cannot be excluded.

Primary care physicians should be aware of the effect of clinical setting on the diagnostic accuracy of gallstones. As far as we know, studies evaluating the diagnostic accuracy of abdominal symptoms in gallstones have not yet been performed in the setting of primary care.

The diagnostic accuracy of single abdominal symptoms was evaluated. In daily practice clinicians will base their diagnosis on a complex of symptoms and signs. Few studies in our meta-analysis performed multivariable analysis[3,5,14]. In our analysis biliary colic, as described in the different studies, included more than one aspect of abdominal pain and might therefore have the best discriminative capacity.

It is doubtful whether further studies on diagnostic accuracy will elucidate the relation between abdominal symptoms and gallstones. Future research on this relation should be directed towards controlled studies on the prognosis of abdominal symptoms, in the clinically relevant setting of primary care. The evaluation of the complex of symptoms of the presenting patients should be emphasized and evaluated.

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2

Accuracy of a combination of abdominal symptoms and signs in the diagnosis of gallstones

Abstract

Objective: *To identify the combination of abdominal symptoms that is most associated with gallstones on sonography.*
Design: *Prospective data collection in patients suspected for gallstones referred for sonography.*
Setting: *General practitioners (n=247) referring patients either to the radiology department of 9 regional hospitals or to a diagnostic service for general practitioners in the Netherlands.*
Subjects: *A total of 221 consecutive patients, aged 18-70 years, with abdominal symptoms and signs suspected for gallstones, without acute cholecystitis or other acute abdominal illnesses.*
Measurements: *Abdominal tenderness, weight and height of the patients were registered as well as the presence and severity of 13 clinical items. Then, the presence of gallstones was determined by sonography, which was interpreted by radiologists blinded to the clinical findings.*
Results: *Forty-two percent (90/221) of patients meeting the entrance criteria had gallstones. Patients with female gender, vomiting, pain RUQ and jaundice more frequently had gallstones on ultrasound, with subgroup prevalences ranging from 20 to 82%. The diagnostic value of the symptoms was comparable in the two different settings, although the prevalence of gallstones differed. The overall discriminative capacity of the prediction model, between patients with and without gallstones was low: estimated area under the ROC-curve 0.64 (95% confidence interval 0.57 to 0.72).*
Conclusions: *Severe pain in the RUQ of the abdomen, vomiting, and jaundice are associated with the presence of gallstones on ultrasound. A large part of the differences in symptomatology between patients with and without gallstones remains unexplained. The decision as to whether or not a patient's symptoms are attributable to gallstones can not be based on the specificity of these symptoms for gallstones.*

Although the prevalence of gallstones is large and cholecystectomy is a frequently performed surgical procedure, decisions concerning the relevant symptoms of gallstone disease remain problematic. This raises the question concerning the specificity of abdominal symptoms for gallstone disease.

Several controlled studies evaluating the diagnostic accuracy of single abdominal symptoms for gallstones have reported variability between studies[1,2]. The estimated sensitivity and specificity was rather limited for most symptoms, when studied in isolation[1,2]. Most of these studies had methodological imperfections ranging from inadequate description of the included patients to lack of blinding of the reader of the ultrasound, but none of these imperfections could explain the variability in diagnostic accuracy[1]. Biliary pain defined as "a steady upper abdominal pain lasting for more than half an hour" was found to be weak but consistently associated with gallstones. The association between nausea or vomiting and gallstones was far more inconsistent[2], and an association with food intolerance and gallstones could be excluded[1].

A physician seeing a patient with abdominal symptoms is more likely to rely on patterns of symptoms than on isolated complaints or single elements in the patient's history. Several factors will increase the strength of suspicion of gallstones, whereas others will decrease the likelihood of gallstone disease. A few studies have examined the diagnostic accuracy of such combinations of symptoms[3,4,5].

Studies on the diagnostic accuracy of abdominal symptoms for gallstones should therefore evaluate combinations of symptoms in order to establish those with the best discriminative capacity. Multivariable modelling can help in this endeavour.

Therefore, we performed a multivariable analysis on prospectively collected data with the aim to identify the combination of abdominal symptoms with the best diagnostic accuracy for gallstones. Because two recent meta-analyses on the diagnostic accuracy of abdominal symptoms and gallstones reported that the diagnostic accuracy of related symptoms varied between different study settings[1,2], we also evaluated the influence of the place of referral on the diagnostic accuracy of combinations of symptoms.

Methods

Study Sample

A total of 400 general practitioners (GPs) in the area of Rotterdam, the Netherlands, were invited to participate in the study; of these, 247 (62%) accepted. All consecutive patients aged 18 to 70 years, who consulted a participating GP – between January 1996 and June 1998 – with abdominal symptoms were eligible for the study. Emergency patients who were suspected for acute cholecystitis or other acute abdominal illnesses were excluded. The GP could choose between two places to refer the patient for sonography of the abdomen. Patients in whom the GP considered the probability of gallstones high were referred to the radiology department of one out of nine local hospitals, all other eligible patients were referred to a GP diagnostic service.

When a GP decided that an eligible patient would be referred to a radiology department: written informed consent was received and a standardised clinical examination was performed to determine abdominal tenderness, location of the pain, weight and length. All patients answered a structured, written questionnaire. These patients were then referred for a standardised ultrasound examination of the upper abdomen.

Alternatively, when the GP decided that an eligible patient should be referred to the GP diagnostic service, patients gave written informed consent at the service, before ultrasonography. A trained medical, fourth-year student performed the standard clinical examination as above and the patients answered the same structured, written questionnaire. All examinations were performed before sonography.

Clinical Examination

Patients were asked about the presence or absence of 13 symptoms during the last month, and for the frequency with which these symptoms had occurred during the last year. These symptoms were: nausea, vomiting, bloating, belching, acid regurgitation, constipation, diarrhoea, flatulence, right upper quadrant abdominal (RUQ) pain, RUQ pain after fatty food intake, RUQ pain lasting more than one hour, jaundice, and fever ≥ 38°C. Answers were elicited on a 4-point scale indicating the severity of the symptom: absent, mild, severe, or very severe. All patients were unaware of the results of the sonography when they filled in the questionnaire.

Reference Standard

Unaware of the subject's medical history, an echographist or a radiologist performed a standardized sonographic examination of the upper abdomen, using real-time sonography with a 3.5 MHz linear transducer. All patients were studied in an overnight fasting state, in supine, left lateral position and, when stone impaction was suspected, in standing position. Gallstones were defined as echogenic masses with shadowing in the gallbladder or bile duct lumen.

Statistical Analysis

All symptoms and signs were initially coded as either present or absent. The presence and the severity of each of the 13 symptoms and signs was then evaluated univariately for an association with the presence of gallstones as identified by ultrasonography, using a Fisher Exact test statistic. To express the diagnostic accuracy of the symptoms and signs, unadjusted diagnostic odds ratios (DORs) with 95% confidence intervals were calculated. The DOR is a function of the true positive rate (TPR) and the false positive rate (FPR): DOR=(TPR/(1-TPR)) / (FPR/(1-FPR)). A DOR of 1.0 indicates no diagnostic value. The DOR is >1.0 if the symptom occurs more often in patients with gallstones than in patients without gallstones, it is <1.0 if the reverse holds.

Multivariable Modelling

All symptoms that were univariately associated with the presence of gallstones ($p<0.25$) were entered into a logistic multivariable regression model, with gallstones detected by sonography as the dependent variable. Adjusted diagnostic odds ratios with asymptotic 95% confidence intervals around the DOR were calculated from the regression coefficients.

To evaluate whether the diagnostic value of the symptoms differed significantly between the two settings, interaction terms between symptoms and place of referral were examined.

Deletion of cases with missing data may cause bias and will increase variance[6]. For 15 patients for whom one clinical characteristic was missing, the most cited answer was imputed. Patients for whom more than one value was missing were excluded from the multivariable analysis (n=7).

The diagnostic accuracy of this prediction model was evaluated by calculating the area under the receiver operating characteristic (ROC) curve[7]. SPSS software was used to perform the analyses[8]. Except for the construction phase of the multivariable model, a p-value of 0.05 or lower was considered to indicate statistical significance.

Results

A total of 221 patients were included in the analysis; of these 162 patients were referred to a radiology department and 59 to the GP diagnostic service. There were significant differences between the two groups. Patients referred to a radiology department more often had vomiting, (severe) RUQ pain, RUQ pain lasting > 1 hour and tenderness of the RUQ, the mean frequency of episodes of symptoms was lower, whereas those referred to a GP diagnostic service were older (Table 1).

Patients referred to the radiology department had a significantly higher (49%) prevalence of gallstones than patients referred to the GP diagnostic service (22%) (Table 1).

The diagnostic value of single abdominal symptoms for gallstones was very low, with the exception of the presence of jaundice (Table 2). Based on the p-value in the univariate analysis, gender, nausea, vomiting, (severe) pain RUQ, pain RUQ provoked by fatty food, fever ≥38°C, and jaundice were included in the logistic regression model. Nausea was strongly related with all other characteristics included and was therefore excluded from the final model. Once adjusted for the effect of the other characteristics, pain RUQ provoked by fatty food and fever ≥38°C were no longer significantly related to gallstones (Table 3). There were no differences in the diagnostic value of these symptoms according to the place of referral: none of the interaction terms was significantly different from zero. Corrected for differences in baseline characteristics of the patients, the prevalence of gallstones was higher in the group referred to the radiology departments than in those referred to the GP service. (Table 3).

The goodness of fit of the final prediction model is presented in Fig. 1. In this figure

Table 1
Frequency of symptoms and signs according to referral

Characteristics	GP diagnostic service (n=59) (%)	Radiology department (n=162) (%)
Age > 40 years	76	59*
Female	70	77
Symptoms		
Nausea	71	71
Vomiting	20	36*
Bloating	76	74
Belching	67	70
Acid regurgitation	51	47
Pain right upper abdomen	59	81*
– Provoked by fatty food	41	51
– Lasting > 1 hour	65	78*
Pain episodes last year, n <10	71	84*
Diarrhoea	47	40
Constipation	41	36
Flatulence	66	74
Fever >38^{0}C	27	30
Jaundice	4	6
Interference with daily activity	66	67
Signs		
Tenderness of abdomen		
– Right upper quadrant	39	74*
Quetlet index (kg/m^2) > 25	62	57
Number with gallstones	22	49*

* Statistically significant difference p<0.05

the probability of gallstones, as predicted by the model is compared with the probability of gallstones as actually observed in our patients. (Goodness of fit test, Hosmer and Lemeshow: Chi-square 6.4, df 7, P=0.49). The ROC shows the true positive rate of the prediction model (sensitivity) versus the false positive rate (1 minus the specificity) for various cut-off values in the estimated probability of gallstones (Fig. 2). The estimated area under the ROC curve was 0.64 (95% confidence interval 0.57 to 0.72).

Even with a score of 0 (none of the symptoms present in men) there was still a 20% risk of finding gallstones on ultrasound.

Table 2
Diagnostic value of unadjusted symptoms and signs for gallstones in patients referred for ultrasound of the upper abdomen because of abdominal symptoms

	sensitivity (%)	specificity (%)	Predictive value symptom present (%) (95% C.I.)*	DOR (95% C.I.)*
Age > 40 years	61	34	40 (32 to 48)	0.8 (0.5 to 1.4)
Female	82	30	40 (38 to 53)	1.9 (1.0 to 3.7)§
Quetlet index (kg/m²) > 25	61	44	46 (35 to 53)	1.3 (0.7 to 2.2)
Symptoms				
Nausea	79	35	47 (39 to 55)	2.0 (1.1 to 3.8)§
Vomiting	42	75	55 (43 to 67)	2.2 (1.2 to 4.0)§
Bloating	79	29	44 (37 to 53)	1.5 (0.8 to 2.9)
Belching	73	33	44 (36 to 52)	1.3 (0.7 to 2.3)
Acid regurgitation	44	50	39 (29 to 49)	0.8 (0.5 to 1.3)
Diarrhoea	44	60	44 (34 to 55)	1.2 (0.7 to 2.0)
Constipation	34	61	39 (28 to 50)	0.8 (0.5 to 1.4)
Flatulence	71	28	42 (34 to 50)	1.0 (0.5 to 1.8)
Severe pain right upper quadrant	80	28	49 (39 to 58)	1.8 (1.0 to 3.2)§
– Provoked by fatty food	55	57	48 (38 to 58)	1.6 (0.9 to 2.7)§
– Lasting > 1 hour	78	28	44 (37 to 52)	1.4 (0.7 to 2.6)
Pain episodes last year, n <10	82	20	42 (26 to 59)	0.9 (0.4 to 1.8)
Fever ≥38°C	34	75	49 (36 to 62)	1.5 (0.8 to 2.7)§
Jaundice	10	98	82 (48 to 98)	6.8 (1.4 to 32.4)§
Signs				
Tenderness of abdomen				
– Right upper quadrant	67	38	42 (35 to 52)	1.3 (0.7 to 2.2)

DOR = Diagnostic Odds Ratio
* 95% confidence interval
§ p<0.25

Table 3
Adjusted diagnostic odds ratio (DOR) for symptoms and signs according to referral status (n=214)

	Beta coefficient	DOR (95 % C.I.)*	Score
Female	0.6	1.9 (0.9 to 3.9)	3
Vomiting	0.6	1.8 (1.0 to 3.5)	3
Pain in right upper quadrant provoked by fatty food	0.09	1.1 (0.6 to 2.0)	0
Severe pain in right upper quadrant	0.4	1.6 (0.9 to 2.8)	2
Fever ≥38°C	0.008	1.0 (0.5 to 2.0)	0
Jaundice	1.9	6.9 (1.3 to 35.8)	9
Setting (radiology department / GP diagnostic service)	1.1	2.9 (1.4 to 6.1)	5

* Diagnostic odds ratio, 95% confidence interval

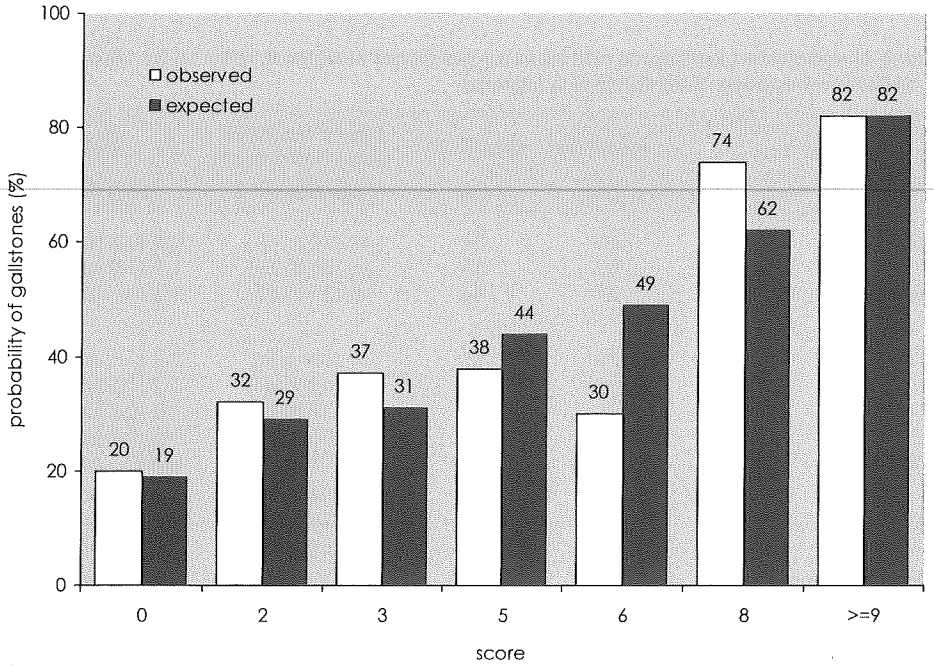

Figure 1
The probability of gallstones according to a score based on the presence of abdominal symptoms, as observed in this study and as predicted by the prediction model.
0: n=20; 2: n=19; 3: n=52; 5: n=58; 6: n=23; 8: n=31; ≥9: n=11.

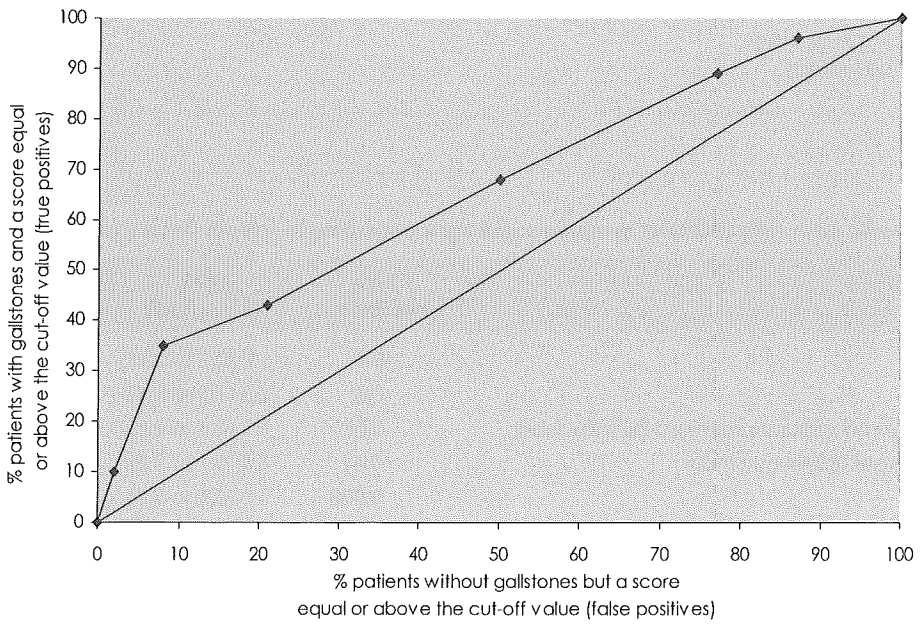

Figure 2
ROC curve of the discriminative capacity of the prediction model. The dots on the ROC-curve refer to a score ≥9, ≥8, ≥6, ≥5, ≥3, ≥2, and ≥0, respectively.

Discussion

We aimed to identify a combination of abdominal symptoms and signs that would predict the presence or absence of gallstones in patients referred by their GP for an ultrasound examination of the upper abdomen. The results showed female gender, vomiting, severe RUQ pain, RUQ pain provoked by fatty food, fever ≥38°C, and jaundice to be associated with the presence of gallstones on ultrasound. Unfortunately, a multivariable prediction model based on these symptoms had low overall discriminative capacity (AUC 0.64; 95% C.I. 0.57 to 0.7).

The risk of gallstones was twice as high in patients referred to a radiology department of a local hospital (49%) than in those sent to a GP diagnostic service (22%). This difference in prevalence of gallstones might be explained by a selection of the patients based on the presence of abdominal symptoms related to gallstones.

It is also possible that the GPs in this study decided to refer the patient because of the presence of symptoms or signs, other than those registered in our study. Referring to the radiology department might be more convenient in patients in which further referral (e.g. to a surgeon) is anticipated. In the prediction model the variable "place of referral" is a black box full of (unknown) factors related to gallstones, used by the GP to estimate the patient's probability of having symptomatic gallstones.

It should be stressed that we studied a selected population. The selection is likely to have influenced the overall discriminative capacity for gallstones of the symptoms[9,10]. It is possible that the prediction model we built has a better discriminative capacity in the unselected set of patients seen by the GP.

The low discriminative capacity of the combination of symptoms found in the present study could also be influenced by the use of sonography as a reference standard. Not all gallstones as detected on ultrasound are symptomatic. Some stones will be detected by chance alone and are in fact asymptomatic. Any such misclassification will cause an underestimation of the discriminative capacity of the diagnostic model presented in this study.

Our findings confirm those reported by others: severe pain in the RUQ of the abdomen is associated with the presence of gallstones. In a screening study, Jørgensen[11] found that a combination of severe, upper right quadratic pain and radiation of the pain to back or shoulder predicted gallstones in 25% of the subjects in which the prevalence of gallstones was 6.2%. Farrell et al.[3] reported that pain lasting for more than 1 hour, any radiating pain and the absence of flatulence were independent predictors of gallstones. We could not confirm the negative relation between flatulence and gallstones. The relation between radiating pain was not evaluated in our study, but was not confirmed by Thijs et al.[5] In a recent systematic review, however, radiating pain was associated with gallstones, although the association was not significant[1].

Earlier studies showed an association between gallstones and food intolerance and pain after fat intake[2]. We found no such associations, nor did two recent studies on this subject[1,5].

The association between vomiting and gallstones is inconsistent[2]; the association we found was not confirmed by Thijs et al.[5] Differences in the extent of gallstone disease in the different groups of patients studied might explain these inconsistencies. In our study the association between vomiting and gallstones was only present in patients with RUQ pain. The prevalence of gallstones was twice as high in patients with RUQ pain who vomited compared to those who did not vomit (68% vs. 39%, respectively). In patients without RUQ pain the prevalence of gallstones did not differ according to the presence or absence of vomiting (39% vs. 31%, respectively). Vomiting should be seen as an accompanying gastrointestinal symptom in severe gallstone disease.

We found no influence of the setting of the study on the diagnostic accuracy of the symptoms studied. Two recent meta analyses[1,2], however, reported such an effect. This finding was confirmed by Thijs et al.[5] Our study differed from the other studies in that we compared two different populations of referred patients whereas the other three studies compared screening studies with clinical studies of referred patients. With more precise selection mechanisms in the referral process, more pronounced differences in diagnostic accuracy are expected. In the present study the difference in extent of disease between patients seen at a GP service and patients seen at a radiology department might have been too small to result in significant differences in diagnostic accuracy.

To summarise, our study confirms the conclusion of Ransohoff and Gracie[12] who reported that the diagnosis of whether gallstones are symptomatic is based primarily on the presence of biliary colic, that is, discrete episodes of severe steady upper abdominal pain that last for more than 1 hour. We hypothesised that vomiting is only related to gallstones in seriously ill patients, and the association between radiating pain and gallstones remains controversial.

Conclusions

Although we found a strong association between jaundice and gallstones, a relation that is probably causal because of its biological plausibility, its relevance for daily clinical practice is limited because of the infrequent occurrence of this symptom in patients suspected for gallstones. In our study only 10 patients reported jaundice, 9 of whom proved to have gallstones on ultrasound.

In the present study 33% (30/90) of the patients with gallstones were referred with abdominal symptoms other than severe upper abdominal pain or jaundice; 18 of these patients were cholecystectomized. The discussion remains whether these patients had asymptomatic gallstones or wether the gallstones caused symptoms other than biliary colic. Perhaps symptoms such as food intolerance, with hardly any discriminative capacity for the presence of gallstones, improve after cholecystectomy. A randomised trial found an improvement of fatty food intolerance after cholecystectomy as well as after shock wave lithotripsy[13]. This might indicate that the pathophysiologic pathway of the abdominal symptoms (irritation of the peritoneum[14], overproduction of prostaglandins[15],

biliary and/or gastric dysmotility[16]) is not unique for gallstones. Gallstones may be a symptom of this underlying defect.

It is doubtful whether further studies on diagnostic accuracy will further clarify the association between abdominal symptoms and gallstones. Future research on this association should be directed towards controlled studies on the prognosis of patients with a diversity of abdominal symptoms, preferably in the clinically relevant setting of primary care.

Until the results of such studies are available, the decision as to whether or not a patient's symptoms are attributable to gallstones cannot be based on the specificity of these symptoms for gallstones.

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3

Abdominal symptoms, do they disappear after cholecystectomy?

A systematic literature review and a controlled prospective study

Abstract

OBJECTIVE: *To identify abdominal symptoms that are likely to disappear after cholecystectomy in patients with gallstones.*

METHODS: *(1) A systematic review of the literature (1966-1998) was performed, using the Medline database in combination with reference checking. Two independent assessors selected studies that had included patients ≥18 years of age. Articles were excluded if symptom relief rates could not be calculated, if follow-up after cholecystectomy was less then one month, or when the included patients were at extraordinary risk for a complicated outcome. Potential differences in relief rates due to patient selection, study design, duration of follow-up, or intervention were analysed using logistic regression. (2) A follow-up study of consecutive patients presenting at their general practitioner with symptoms suggestive for gallstone disease. With a self-administered questionnaire 13 abdominal symptoms were registered at inclusion and after a median follow-up of 14 months. Symptom relief rates were calculated and compared between operated patients with gallstones and patients without gallstones.*

RESULTS: *Relief rates for biliary pain and vomiting were high in patients operated for gallstones as well as in those without gallstones (86% versus 80% and 90% versus 73%, respectively). For upper abdominal pain and upper abdominal pain after fatty food intake, relief rates were 70% in the operated patients compared to 54% and 60%, respectively, in patients without gallstones. For all other symptoms relief rates equalled the rates of persistence of symptoms in both groups. These findings were comparable with the findings of the systematic literature review after adjusting for differences in patient selection.*

CONCLUSION: *In almost all patients with gallstones biliary pain disappeared after cholecystectomy. This finding was not specific for cholecystectomized patients. Relief rates of other isolated symptoms were low and comparable to relief rates in a control group of patients without gallstones. A proper evaluation of the effectiveness of cholecystectomy in terms of abdominal symptom relief rates requires a randomised trial.*

There is general agreement that symptomatic gallbladder stones should be treated[1]. Yet the decision whether abdominal symptoms are related to gallbladder stones remains a diagnostic challenge for the clinician. There is little doubt that severe, steady upper abdominal pain lasting more than 1-hour indicates gallbladder stones[2], but controversy exits about a causal relationship between other gastrointestinal symptoms and gallbladder stones. Although few general practitioners will consider gallstones in a patient with only dyspeptic symptoms the diagnosis of gallstones will become more likely when upper abdominal pain accompanies these symptoms. The key questions are whether relief of symptoms after cholecystectomy can be predicted, and may we assume that these symptoms disappear due to cholecystectomy?

Studies evaluating the clinical outcome after cholecystectomy have presented varying results, partly due to differences in the design of these studies[3]. In one prospective study 37% of the cholecystectomized patients did not experience relief of symptoms, including abdominal pain[4]. In a retrospective study of patient outcome after cholecystectomy abdominal bloating, dyspepsia, heartburn, fat intolerance, nausea, and vomiting significantly decreased after cholecystectomy. The prevalence of these symptoms after cholecystectomy was comparable with the prevalence in a group of patients with illnesses unrelated to gallstones[3].

A comparison of abdominal symptoms before and after cholecystectomy makes it difficult to attribute improvement exclusively to the surgical procedure. The natural history of a non-related gastro-intestinal disease (e.g. functional dyspepsia) may well explain improvement. To allow for a valid evaluation of treatment effectiveness, symptom relief rates of abdominal symptoms should be compared between cholecystectomized patients and a comparable control group with identical follow-up.

The aim of this study was to identify abdominal symptoms that are most likely to disappear after cholecystectomy in patients with gallstones. For this purpose we performed a systematic review of the literature. Our second aim was to compare the symptom relief rate one year after cholecystectomy with relief rates in a control group of patients without gallstones, who had presented to their general practitioner with symptoms suggestive for gallstone disease. This was evaluated in a controlled prospective study.

Methods

Systematic Review

A systematic literature search was conducted using the Medline database (January 1966 to January 1999) of all English-, French-, Dutch- and German-language articles investigating the symptomatic outcome of cholecystectomy for gallstone disease. Combinations of the search keys "cholelithiasis", "cholecystectomy", "abdominal pain" and "dyspepsia" as MeSH headings with "symptom", "sign", "gallstone", and "gall stone" as (part of) text words were used. Additional references were obtained from the bibliographies of review articles and original papers. Articles were excluded from further consideration if

the follow-up after cholecystectomy was less then one month, if the included patients were younger then 18 years of age or if the included patients were at an extraordinary risk for a complicated outcome, such as when the presence of diabetes mellitus was used as an additional criteria for inclusion. Two independent readers (M.Y.B. and T.o.H.) reviewed the abstracts of all publications. Cases of disagreement were resolved by consensus. A standard form was used to extract pertinent data from the included articles (Table 1).

- *Analysis*

Relief rates after cholecystectomy were calculated for each symptom. The relief rate was defined as the number of patients in which the symptom had disappeared post-operatively, divided by the number of patients exhibiting that same symptom pre-operatively. Persistence rates after cholecystectomy were calculated as one minus the relief rate. For each symptom the *de novo* rate was calculated as the number of patients who developed the symptom for the first time post-operatively divided by the number of patients without the symptom pre-operatively.

In the studies identified through the systematic search of the literature we examined differences in study results related to the following potential explanatory variables[5].

- *Recall-bias*

In a retrospective study design, where patients are asked post-operatively about their pre-operative symptoms, symptom recall might be less accurate than in prospective studies, where patients are asked before cholecystectomy about their actual symptoms.

- *Patient selection*

Studies that included only patients with an elective cholecystectomy were compared with studies that evaluated both patients with an acute and patients with an elective cholecystectomy.

- *The duration of follow-up*

The duration of follow-up was evaluated in order to preclude the "placebo" effect of the cholecystectomy. Studies with a follow-up ≤12 months were compared with studies with a follow-up greater than 12 months.

- *Intervention*

The choice of intervention, laparoscopic or open cholecystectomy, was also evaluated, although we expected little impact on the outcome of the studies.

As a measure for heterogeneity the chi-square test statistic was used, with n-1 degrees of freedom, n being the number of studies. To evaluate the effect of the variables related to heterogeneity on the results, univariate logistic regression was performed with the symptom relief rate as the dependent variable and the explanatory variables as the independent variables. All variables related to symptom relief with a p-value of 0.25 or lower were included in a multivariable analysis whenever the number of studies allowed this.

Pooled estimates of the symptom relief rates with 95% confidence intervals were calculated according to the random effects model of Dersimonian and Laird[6]. All computations were performed with SPSS for Windows software, version 7.5[7].

Follow-up study

A total of 400 general practitioners (GPs) in the area of Rotterdam, the Netherlands, were invited to participate in the follow-up study, of which 247 (62%) GPs accepted the invitation. All consecutive patients aged 18 years and older who consulted a participating GP between January 1996 and June 1998 with abdominal symptoms suggestive of gallstone disease were eligible for the study. Emergency patients who were suspected of acute cholecystitis or other acute abdominal illnesses were excluded.

Eligible patients were asked for written informed consent. In all included patients, a standardised clinical examination was performed to determine abdominal tenderness, location of pain, weight and length. In a structured written questionnaire patients were asked for the presence or absence of 13 abdominal symptoms during the last month. Patients were referred either to the radiology department of one out of nine local hospitals or to a GP diagnostic service for a standardised ultrasonographic examination of the upper abdomen.

One year after cholecystectomy and one year after inclusion for patients who had no surgery, a copy of the same questionnaire was sent by mail. Non-responders received a reminder by mail and a second reminder by telephone within one month. The research ethics committee of the University Hospital Rotterdam approved the study protocol

Results

Systematic review

Our search strategy yielded 542 publications, of which 516 could not be included; 402 were unrelated to the subject of our study; 35 because treatment of gallstones was not cholecystectomy; 26 because the patients studied were under the age of 18 years; 42 because the patients studied were at an extraordinary risk for a complicated outcome; 12 because no original data were used and 8 because no preoperative measurement of the presence of symptoms was performed. Seven additional publications were identified from the reference lists.

On 5 articles the readers initially disagreed about inclusion. Consensus was reached in all cases. Of the remaining 33 publications 11 articles had to be excluded; in 5 the presentation of the results precluded a comparison between pre- and postoperative symptoms[8-12], in 3 the subject of the article was not related to the subject under study[13-15], in one follow-up was restricted to patients with post-operative symptoms only[16], and the data of 2 studies had already been presented in another included study[17,18]. Thus 22 articles were available for the analysis.

Table 1
Characteristics of 22 studies included in the analysis of symptom relief after cholecystectomy

Author (ref.)	Publication year	Intervention	Study design	Inclusion criteria.	Exclusion criteria	Included patients (n)	Sex M/F	Mean age (years)	Measurement preoperative	Measurement postoperative	Mean follow-up (months)(range)	Loss to fup n (%)
Bouchier (19)	'68	open	pros	?	–	17	6/11	56 (34-68)	non structured interview	non structured interview	12 (6-24)	0 (0)
Rhind (20)	'68	open	retro	dyspepsia, biliary colic, hiatus hernia, elective	peptic ulcer, cbds*	56	?	?	none	interview	12	?
Southam (21)	'68	open	pros	gallstones and oesophageal symptoms, elective	?	12	?	?	non structured interview	non structured interview	?	0 (0)
Johnson (22)	'71	open	retro	proven stones at operation, normal cbd**, elective	peptic ulcer, pancreatitis, hiatus hernia, preoperative jaundice, exploration of cbd, sfincterotomy or other abdominal operation	108	35/73	50.7	none	structured interview or postal questionnaire.	15 (3-42)	0 (0)
Gunn (23)	'72	open	pros	gallstones, elective	pathologic conditions	107	19/88	47.5	structured (?) interview	structured (?) interview	18 (12-24)	0 (0)
Kingston (24)	'75	open	pros	gallstones and acute cholecystitis (52), elective and acute	?	100	25/75	53 (17-80)	interview	interview	13 (3-36)	0 (0)
Feretis (25)	'83	open	pros	?	?	47	11/36	46 (23-69)	?	?	6 (3-6)	?
Ross (26)	'87	open	pros	gallstones, no emergency, elective		93	25/99	58 (39-76)	questionnaire and inteview	questionnaire and interview	24	31 (24)
Gilliland (27)	'90	open	retro	Symptomatic gallstones, elective	non-elective exploration of cbd	525	188/462	53 (16-86)	medical records	questionnaire by telephone or mail	45 (15-79)	125 (19)
Paul (28)	'91	open	pros	symptomatic gallstones, elective	gastrointestinal comorbidity	51	13/47	56 (21-78)	structured interview	structured interview	4 (1-12)	9 (15)

Bates (4)	'91	open	pros	gallstones with upper abdominal pain or complications, elective and acute	--	278	82/196	53 (20-90)	self-administered questionnaire	self-administered questionnaire	11	14 (5)
Jørgensen (29)	'91	open	pros	symptomatic gallstones, elective	asymptomatic gallstones	115	40/75	58 (18-86)	structured interview	structured interview	9 (6-12)	7 (6)
Vander Velpen (30)	'93	open (80) lapar. (80)	retro	symptomatic gallstones ?	cbds	56 O 68 L	46/78	62 (32-87)	none	self-administered questionnaire	11 (6-30)	36 (23)
Qureshi (31)	'93	lapar.	retro	biliary colic, chronic +acute cholecystitis, pancreatitis, elective and acute	asymptomatic gallstones	100	23/77	47 ± 13.1	none	questionnaire	12 (10-19)	0 (0)
Rädecke (32)	'93	open	pros	symptomatic gallstones acute+elective	previous operation gallbladder, malignancy	80	33/47	56 (21-86)	interview, not standardised	interview, not standardised	14 (6-28)	25 (24)
Scriven (33)	'93	open	pros	gallstones, elective	?	75	?	?	self-administered questionnaire	self-administered questionnaire	12	2 (3)
Plaisier (34)	'94	open lapar. (5)	pros	symptomatic gallstones, elective	asymptomatic gallstones, complicated gallstone disease	22	6/20	49.8 ± 12.8	pain diarys self-administered questionnaire	pain diarys, self-administered questionnaire, inteview, telephone	18 (12-24)	4 (15)
Ure (35)	'95	lapar.	pros	symptomatic gallstones, elective	> 60pnt Talley-score, cancer of gallbladder, other scopic surgery	468	111/357	50 (47.7-52.3)	self-administered questionnaire	self-administered questionnaire.	19 (11.5-32)	0 (0)
Fenster (36)	'95	lapar.	pros	?	?	164	58/167	50 (12-79)	interview, questionnaire	Interview, questionnaire	3	24 (13)
Luman (37)	'96	lapar.	pros	gallstones, elective and acute	open cholecystectomy	84	19/78	50.9 (19-85)	standardised questionnaire, interview	standardised questionnaire, Interview	7 (6-10)	0
Farsakh (38)	'96	?	pros	gallstones, elective	gastric surgery, severe illness	30	5/25	43.8 (22-70)	interview	interview	6 (3-9)	0
Gui (3)	'98	open (35) lapar. (57)	retro	symptomatic gallstones, elective	?	92	22/70	51.2 (24-84)	none	structured interview	31 (12-83)	0

Intervention: lapar. = laparoscopic cholecystectomy

Study design: Pros = prospective
Retro = retrospective

Inclusion criteria: CBD = Common bile duct
CBDS = Common Bile Duct Stones

The methodological quality of the studies was low. Eight publications (35%) did not provide enough information to enable a proper interpretation of the results[19-21,25,30,33,36,38]. Four of these studies had been published before 1990. (Table 1).

Follow-up ranged from 3 to 45 months in the 20 studies that reported it, with a median duration of follow-up of 12.5 months. Nineteen studies reported age and sex of the study population. Age ranged from 43.8 to 62 years, with a median of 51.8 years. The proportion of women ranged from 59% to 87%, with a median of 76%.

Patient selection could be related to a systematic difference in study results. Symptom relief rates were consistently higher in studies that also included acute cholecystectomies, compared to studies that evaluated elective cholecystectomies only (Fig.1). For food intolerance the duration of follow-up influenced the results: studies with a follow-up ≤12 months did report higher relief rates for food intolerance (83% (74 to 92%)) compared to studies with a follow up of more than twelve months (70% (65 to 73%)). The other potential explanatory variables of study design mentioned above could not be related to symptom relief.

The course of the symptom "biliary pain" could be evaluated in 9 studies (Fig. 1). One study included elective and acute cholecystectomies[32]. In most studies biliary colic was defined as severe (steady) pain in the upper abdomen or epigastrium lasting >30 minutes. Only the study of Scriven *et al.*[33] used a different definition for biliary colic without restrictions for severity and duration of the pain. Scriven *et al.* found a symptom relief rate of 73%. The pooled symptom relief rate was 91% (95% confidence interval 85 to 96%). Five studies evaluated the postoperative incidence of biliary pain in patients without preoperative biliary pain. The *de novo* rate ranged from 0%[3] to 38%[33].

The course of the symptom "upper abdominal pain" was evaluated in 13 studies (Fig. 1). The symptom relief rate could be calculated in 11 studies. The relief rate for upper abdominal pain ranged from 57%[33] to 88%[32].

For upper abdominal pain the relief rates showed some heterogeneity. In studies including only patients with an elective cholecystectomy the pooled relief rate for upper abdominal pain was significantly lower than in studies that also included patients with an acute cholecystectomy: 72% (66-77%) versus 86% (83-91%), respectively. Eight studies evaluated the post-operative incidence of upper abdominal pain. The *de novo* rate ranged from 0%[19,31,37] to 15%[30].

Nine studies evaluated whether dyspepsia improved after cholecystectomy (Fig. 1). Dyspepsia was defined as the presence of three or more dyspeptic symptoms out of six or seven. These symptoms included belching, flatulence, nausea, and intolerance to fatty food, bloating of the abdomen, epigastric discomfort and acid regurgitation. Relief rates for dyspepsia were heterogeneous and varied from 46%[22,36] to 89%[32]. Most of the heterogeneity could be explained by differences in the selection of patients. In studies of patients that had undergone an elective cholecystectomy the pooled symptom relief rate was significantly lower than in studies that included also acute cholecystectomies, 56% (46 to 67%) versus 82% (78 to 86%). Four studies evaluated the post-operative incidence

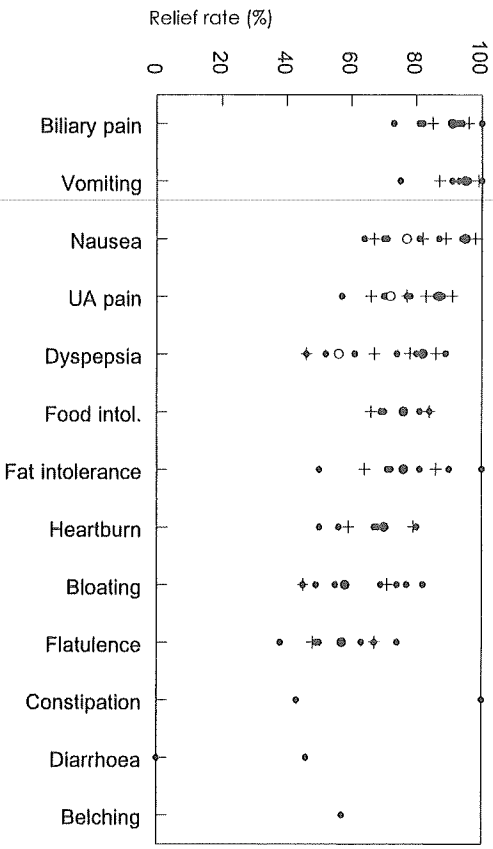

Figure 1
Each dot represents the estimate of a symptom relief rate of one article. The mean symptom relief rates are presented with 95% confidence intervals (+●+). For upper abdominal (UA) pain, dyspepsia and nausea, the mean relief rates and 95% CI for studies selecting elective cholecystectomies (+o+) and for studies selecting also acute cholecystectomies (+●+), are given separately.

of dyspepsia. The *de novo* rate ranged from 0%[22] to 12%[3].

The symptom relief rates for all other abdominal symptoms studied are presented in Fig. 1. For belching (n=1), diarrhoea (n=2) and constipation (n=2) no pooled estimates of the relief rates could be calculated due to the large heterogeneity in a small number of studies.

Follow-up study

In total 233 patients could be included in our own follow-up study, 205 (88%) of whom responded to the follow-up questionnaire. In this group, 95 patients (46%) had gallstones and 73 of them (77%) were cholecystectomized. Twelve of the 28 non-responders had gallstones and were operated. One patient died of hepatocellulair carcinoma; all others had either moved to an unknown address (n=5) or did not want to respond. The non-responders did not differ from the analysed patients as far as age and sex were concerned. Non-responders had more acid regurgitation than responders (71% versus 47%; p=0.01).

Table 2
Patient characteristics in our own follow-up study

	Operated patients with gallstones (n=73)	Patients without gallstones (n=110)
Age in years, (median)(range)	43.5 (17 to 79)	47.5 (21 to 81)
Women n (%)	63 (86)	80 (73)
Follow-up in months, (median) (range)	14 (11 to 34)	12.5 (11 to 24)
Loss to follow-up n (%)	12 (14)	16 (13)

Hundred and ten patients did not have gallstones on ultrasound. There were no differences in median age, sex distribution, and duration of follow-up or loss to follow-up between the operated patients and the patients without gallstones (Table 2).

The median time between study inclusion and cholecystectomy was 19 days; 63% of the patients were operated within one month, 80% within two months and one patient after one year. The preoperative frequency of the symptoms and symptom relief rates are presented in Table 3. The frequency of biliary pain, upper abdominal pain, dyspepsia, belching, upper abdominal pain after fatty food intake, nausea and vomiting was higher in the patients operated for gallstones. The frequency of acid regurgitation, bloating, flatulence, constipation and diarrhoea was similar in both groups. For all symptoms relief rates were higher in the patients operated for gallstones, except for acid regurgitation and diarrhoea. For these symptoms the relief rates were comparable in the control group. Except for flatulence and constipation none of these differences did reach statistical significance. In the patients operated for gallstones, however, the *de novo* rates of flatulence were higher than the relief rates of this symptom. Except for biliary pain in the patients operated for gallstones all symptoms occurred *de novo* in patients who previously did not have the symptom. The de novo rates were comparable in both groups (Table 3).

Discussion

In a systematic review of studies evaluating the effect of cholecystectomy in terms of the disappearance of pre-operative symptoms, consistently high relief rates after cholecystectomy were reported for biliary pain. The relief rates for upper abdominal pain, dyspepsia and nausea showed more heterogeneity. The finding that higher relief rates for upper abdominal pain, dyspepsia, and nausea were reported in studies including also acute cholecystectomies may indicate a dose-response like relation between these symptoms and gallstones. The more extended the disease, the stronger the association between stones and these symptoms will be.

For dyspepsia, however, this is not a plausible conclusion. Dyspepsia, defined as at least 3 abdominal symptoms out of seven, is a syndrome rather than a symptom. Talley

Table 3
Frequency, relief rates and *de novo* rates of abdominal symptoms in patients operated for gallstones and patients without gallstones

	Frequency pre-operative in patients with gallstones (n=73)*	Frequency at inclusion in patients without gallstones (n=110)*	Symptom relief n (%, 95% CI**) (n=73)	Symptom relief n (%, 95% CI**) (n=110)	Symptoms *de novo* n (%, 95% CI**) (n=73)	Symptoms *de novo* n (%, 95% CI**) (n=110)
Biliary pain	44/73	44/102	38 (86, 73-95)	35 (80, 65-90)	0 (0, 0-12)	3 (5, 1-14)
Upper abdominal pain	65/73	79/103	49 (75, 63-85)	43 (54, 43-66)	1 (13, 0.3-53)	8 (33, 16-55)
Dyspepsia	61/73	67/104	30 (49, 36-62)	16 (24, 14-36)	1 (8, 0.2-39)	6 (16, 6-32)
Belching	56/72	70/108	24 (43, 30-57)	21 (30, 20-42)	2 (13, 2-38)	6 (16, 6-31)
A feeling of fullness	56/72	74/106	33 (59, 45-72)	26 (35, 24-47)	5 (31, 11-59)	10 (31, 16-50)
Upper abdominal pain after fatty food intake	46/73	43/106	32 (70, 54-82)	26 (60, 44-75)	5 (19, 6-38)	16 (25, 15-38)
Nausea	58/70	69/107	39 (67, 54-79)	35 (51, 38-63)	2 (17, 2-48)	7 (18, 8-34)
Flatulence	47/73	78/109	**18 (38, 25-54)**	**10 (13, 6-22)**	10 (39, 20-59)	8 (26, 12-45)
Vomiting	39/71	22/103	35 (90, 76-97)	16 (73, 50-89)	4 (13, 4-29)	8 (10, 4-19)
Acid regurgitation	37/73	50/107	13 (35, 20-53)	17 (34, 21-49)	6 (17, 6-33)	13 (23, 13-36)
Diarrhoea	26/73	44/107	6 (23, 9-44)	16 (36, 22-52)	12 (26, 14-40)	12 (19, 10-31)
Constipation	29/72	41/106	**19 (66, 46-82)**	**10 (24, 12-40)**	5 (12, 4-25)	17 (26, 16-39)

* not all patients answered all questions; ** 95% confidence interval
Bold = statistical significant difference between relief rates in patients operated for gallstones and patients without gallstones

et al. reported a placebo response in functional dyspepsia (that is dyspepsia without a biochemical or structural explanation) of almost 70%[39]. This is comparable to the pooled relief rate for dyspepsia in the studies including elective cholecystctomies only: 56% (46-67%). In contrast, dyspeptic symptoms, most likely nausea, may accompany upper abdominal pain in cases of more extended gallstone disease.

The finding that studies with a short follow-up period reported higher relief rates for food intolerance compared to studies with a follow up of 12 months or more can be explained by a placebo effect of the operation. Patients expect food intolerance to improve because of the explicit relation that is often claimed between food intolerance and gallstones. Our finding weakens the evidence for this putative relation.

The variabiltiy in symptom relief rates as reported by others may be explained by differences in the methods for evaluation used, wording of questionnaires, varying duration of follow-up, patient case mix and differences in the strategies used for the analysis (symptom frequencies or symptom relief rates). In this review some of the differences in the results of the studies could be explained by the selection of patients in the studies. Thirty five percent of the included studies lacked information about characteristics of study design, like selection of their study population etc. This might have influenced the results of the individual studies in an unpredictable way. Because there were only few real outliers we think poor methodology might have influenced precision but not the direction of the associations found.

In a prospective study in patients presenting at their GP with abdominal symptoms suggestive for gallstone disease, we determined the one-year symptom relief rate after cholecystectomy. The results were compared with the symptom relief rates in patients with comparable symptoms but without gallstones on ultrasound examination.

The presence of a control group of patients without gallstones allowed us to evaluate the specificity of our findings for gallstone disease. Biliary pain is said to be the most specific symptom caused by gallstones. In our study more patients operated for gallstones reported biliary pain compared to the control group (60% versus 43%) but relief rates were almost the same (86% versus 80%). This finding shows that gallstones do not exclusively cause biliary pain. Nor can symptom relief exclusively be attributed to gallstone removal. It should also be noted that 40% of the operated patients did not report biliary pain.

For upper abdominal pain, upper abdominal pain after fatty food intake, nausea and constipation the postoperative relief rates were about 70%. In the patients without gallstones these rates varied between 25-54%.

For acid regurgitation and diarrhoea, relief rates were lower in the operated patients then in the patients without gallstones. This finding makes a causal relation between gallstones and these symptoms unlikely. A positive association between flatulence and gallstone disease was made very unlikely, because the relief rates in both groups were as high as the de novo rates.

The results of the prospective study were in accordance with the results of the systematic literature review. Only the high relief rate for constipation found in the prospective study could not be confirmed.

Both the control group and the cholecystectomized patients had presented themselves at their GP with symptoms suggestive for gallstone disease and were followed over a comparable period of time, yet it can successfully be argued that the control group in our study is not comparable with patients after cholecystectomy for gallstone disease. Furthermore we do not know whether the control patients were medically treated. The best control group would have been a group of patients with gallstones randomly selected not to have cholecystectomy.

Can relief of symptoms after cholecystectomy be predicted?

From this follow-up study and the systematic review of the available literature we can conclude that biliary pain will disappear after cholecystectomy in about ninety percent of patients with gallstones. Yet comparable symptom relief rates were also found in a control group of patients with similar symptoms but without gallstones.

In patients with a firm diagnosis of symptomatic gallstones, in which an acute cholecystectomy is indicated, for example in a patient with acute cholecystitis, accompanying abdominal symptoms like nausea and vomiting have a high chance of improvement after cholecystectomy. In patients where the diagnosis of symptomatic gallstones is less certain – that is the group of patients where the clinician is confronted with a choice between operation and watchful waiting – a symptomfree outcome after cholecystectomy can insufficiently be predicted by single pre-operative symptoms. Simple upper abdominal pain and upper abdominal pain after fatty food intake have relief rates of about seventy percent. Thirty percent of the patients operated for this indication will have persisting pain after cholecystectomy. For abdominal symptoms like dyspepsia, bloating, flatulence and food intolerance the relief rates after cholecystectomy are comparable with the relief rates after watchful waiting.

We feel that the statement that symptomatic gallstones should be treated remains a sledgehammer argument as long as it is unknown which symptoms are likely to disappear after cholecystectomy, due to this surgical procedure. A proper evaluation of the effectiveness of cholecystectomy in terms of abdominal symptom relief rate requires a randomised trial, comparing patient outcome after cholecystectomy with patient outcome after watchful waiting[41]. If such a trial has a sufficient sample size, patient characteristics can be explored for their relation with gallstone disease, successfully treated by cholecystectomy. If such a trial is not feasible the complex of symptoms and signs should be evaluated for its prognostic value on post-operative outcome, rather than single, separate symptoms. Findings on ultrasound, such as the number and size of the stones[42], stone impaction and thickness of the gallbladder wall[3] may have additional value in predicting the clinical outcome of cholecystectomy.

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4

Can sonography predict relief of upper abdominal pain after laparoscopic cholecystectomy?

A prospective study

Abstract

BACKGROUND: *Gallbladder stones are commonly found at sonography for upper abdominal pain. The purpose of this prospective study was to determine whether sonographic findings can predict relief of abdominal pain after cholecystectomy.*

METHODS: *General practitioners referred 233 patients with symptoms suggestive of gallbladder stones for abdominal sonography. Preoperative sonographic parameters were evaluated by univariate and multivariate analysis using the relief of upper abdominal pain as the dependent variable.*

RESULTS: *Gallbladder stones were present in 107 patients. Cholecystectomy was done in 85 of these patients. Follow up was available in 73 of the operated patients. In 65 of these patients, preoperative upper abdominal pain was present. After a median follow up after cholecystectomy of 14 months (range 11 to 34 months), 75% (49/65) of patients was free of upper abdominal pain. In the univariate analysis, the presence of the sonographic signs of stone impaction in the gallbladder neck or cystic duct and/or thickened gallbladder wall was significantly related to relief of upper abdominal pain after cholecystectomy (odds ratio 4.0, 95% confidence interval 1.1 to 14.2). Grit in the gallbladder on sonography was significantly associated with pain persistence (OR 0.3, 95% CI 0.1 to 1.0). In the multivariable analysis none of these relations reached statistical significance. In 51% of the patients in our study, no thickened gallbladder wall or stone impaction was found. If these patients did not have a laparoscopic cholecystectomy, the upper abdominal pain rate in the operated group would fall from 25% to 12.5%.*

CONCLUSION: *This prospective study showed that sonographic signs of thickened gallbladder wall or impaction were associated with relief of upper abdominal pain after cholecystectomy. Grit found in the gallbladder on the preoperative sonography was associated with persistence of upper abdominal pain. Sonography appears therefore of value in the selection of patients with gallbladder stones for cholecystectomy.*

Laparoscopic cholecystectomy (LC) is the standard treatment of symptomatic gallbladder stones[1,2,4,5,7,10,13,14,16]. Severe upper abdominal pain is the symptom most closely related to gallstones[22]. It is expected that patients with severe upper abdominal pain or related symptoms will be relieved of pain after cholecystectomy. However of all patients who had cholecystectomy, 12 to 47% had no relief of symptoms during a follow-up period of 24 to 120 months[6,8,12,18,19,21,23]. The outcome of surgery in patients with gallstones, without signs of cholestasis and/or cholecystitis is difficult to predict[11,19]. A method to predict outcome of cholecystectomy would be valuable for the patient. Sonography can, in addition to detecting gallstones, assess the size of the gallbladder, wall thickness, size of the stones and presence of echogenic bile or stone impaction. To our knowledge no prospective study has been reported relating findings of sonography of the gallbladder with outcome of cholecystectomy. In a retrospective study, Gui *et al.* found thick-walled gallbladder on ultrasound to be associated with pain-free outcome after cholecystectomy[8]. In a retrospective study, patients with grit (stones ≤3 mm) in the gallbladder on preoperative sonographic examination had only a fifty-fifty chance of pain relief after cholecystectomy[23].

The purpose of this prospective study was to determine whether sonographic features of the gallbladder could predict relief of upper abdominal pain after laparoscopic cholecystectomy.

Materials and methods

Study design

Four hundred general practitioners (GP), practising in the Rotterdam area of the Netherlands, were asked to participate in the study. Two hundred forty seven (62%) agreed to participate. All consecutive patients aged 18 years and older who consulted a participating GP between January 1996 and June 1998 with abdominal symptoms and in whom the GP considered the possibility of gallbladder stones, were eligible for the study. Patients suspected of acute cholecystitis or other acute abdominal illnesses were excluded.

All patients were asked for written informed consent (n=233). Consenting patients were referred to a primary diagnostic service centre or a radiology department of one of nine local hospitals for an ultrasound examination of the upper abdomen. Before sonography, the patient filled out a structured self-administered questionnaire on the presence or absence of 13 abdominal symptoms during the last month. The severity of these symptoms was recorded on a 4-point scale, anchored as absent, mild, severe, or very severe. Upper abdominal pain included all reported upper abdominal pain independent of severity and duration, except upper abdominal pain that only occurred after fatty food intake. One year after surgery, an identical questionnaire was sent to all patients.

The research ethics committee of the University Hospital Rotterdam approved the study protocol.

Sonographic examination

The sonographic examinations were performed either by radiologists, senior radiological residents or experienced radiology technicians. All patients were examined in a fasting state with a 3.5 MHz scanner according to the following standardised protocol: Patients were placed in a supine position and on their left side. When stone impaction was suspected patients were placed in an upright position.

The following parameters were assessed: gallbladder size (normal, contracted, defined as collapsed gallbladder filled with stones, or distended gallbladder, defined as diameter of ≥4.5 cm), thickened gallbladder wall of ≥3 mm, number and size of stones (grit was defined as stones ≤3 mm), echogenic bile, and impaction of stones in the gallbladder neck or cystic duct. A combination of a thickened gallbladder wall or stone impaction, both as plausible indicators of symptomatic gallstones, was separately analysed. The diameter of the gallbladder was calculated as the maximum diameter perpendicular to the longitudinal axis. All items were scored on a structured form.

Statistical Analysis

Upper abdominal pain after cholecystectomy was the primary outcome parameter. The postoperative pain relief rate was defined as the relative number of patients in whom upper abdominal pain was absent postoperatively, divided by the number of patients exhibiting the symptom preoperatively. The sonographic findings were compared with the presence or absence of postoperative pain using the chi-square test with Yates correction. Crude odds ratios (OR) were calculated with 95% confidence intervals (CI). Variables significant at $P<0.05$ were considered to be predictive of symptomatic outcome with reference to postoperative pain.

Variables significant at $P<0.25$ were included in a multivariable logistic regression to assess the independent relationship to upper abdominal pain after cholecystectomy. Deletion of cases with missing data may cause bias and will increase variance[9]. For patients for whom one pre-operative clinical characteristic was missing and for patients for whom one post-operative finding was missing, the most cited answer was imputed. Patients for whom more than one value was missing were excluded from the multivariable analysis.

The Statistical Package for the Social Sciences 7.5 (SPSS Inc. Chicago, IL, USA) was used for statistical computations.

Results

Gallbladder stones were present in 107 patients. Cholecystectomy was performed in 85 of these patients, of whom 73 patients had follow up. In 65 of these patients, the indication for cholecystectomy was upper abdominal pain. In 8 patients dyspepsia was the indication for cholecystectomy. Of these patients, one patient had no sonographic find-

ings, two had wall thickness ≥3 mm and stone impaction, one had a contracted gallbladder and stone impaction. All others either had wall thickening (2), stone impaction (1), or grit (1). One patient with stone impaction was completely symptom free after cholecystectomy. In 12 patients follow up was not available; in all these patients the indication for cholecystectomy was upper abdominal pain.

Sixty-five operated patients suffered from pre-operative upper abdominal pain. These patients had the following characteristics: male/female ratio 8/57, mean age 42.9 years (range 18 to 79). No significant differences were found between the groups of gallbladder stone patients with (n=65) and without (n=12) follow up after cholecystectomy, as far as mean age, male/female ratio, distribution of sonographic signs, and time between sonography and cholecystectomy were concerned. More patients without follow up had fever and diarrhoea (75% versus 36%;p=0.003 and 67% versus 36%; p=0.04, respectively).

The median time between the onset of upper abdominal pain and sonography was 1 day (range 1-15 days). In 63% of the patients the interval between sonography and surgery was less than one month. For 80% it was less than 2 months (range 0-405 days). The median follow up after cholecystectomy was 14 months (range 11 to 34 months). Forty-nine out of sixty-five (75%) patients were free of upper abdominal pain after cholecystectomy.

In the (univariate) analysis, the presence of the sonographic signs of stone impaction

Table 1
Number of patients with sonographic sign (N), percentage of patients with relief of upper abdominal pain, Odds Ratio (OR) with 95% Confidence Intervals (CI).

		N	Pain relief %	OR	95% CI
Gallbladder size#	Normal (<4.5cm)	51	74.5	1	
	Contracted	7	57.1	0.5	(0.1 to 2.3)
	Distended (≥4.5cm)	7	100	*	
Thickness of wall (mm)	≤ 2	42	69.0	1	
	≥ 3	23	87.0	3.0[b]	0.8 to 11.9
Diameter of stones (mm)	≥ 4	42	83.3	1	
	≤ 3 (grit)	23	60.9	0.3[a]	0.1 to 1.0
Number of stones	1	15	73.4	1	
	> 1	50	76.0	1.2	0.3 to 4.3
Echogenic bile	No	53	73.6	1	
	Yes	12	83.3	1.8	0.4 to 9.2
Stone impaction	No	45	68.9	1	
	Yes	20	90.0	4.1[b]	0.8 to 20.0
Stone impaction and/or Thickened wall ≥ 3 mm	No	33	63.6	1	
	Yes	32	87.5	4.0[a]	1.1 to 14.2
Total		65	75.4		

A normal gallbladder size was taken as the reference category
* The relative risk could not be calculated because one of the cells is empty
[a] p<0.05, [b] p<0.25

and/or a thickened gallbladder wall was significantly related to relief of upper abdominal pain after cholecystectomy (OR 4.0, 95% CI 1.1 to 14.2) (Table 1). Although all patients with gallbladder distension were free of upper abdominal pain after cholecystectomy, this relation did not reach the level of significance. A sonographic sign significantly associated with persistent pain was the presence of grit (OR 0.3, 95% CI 0.1-1.0). Of the patients with grit (n=23) only 3 patients had no stones greater than 3 mm. In the multivariable analysis none of the relations mentioned above reached statistical significance (stone impaction: OR 2.9, 95% CI 0.56 to 15.4, P=0.2; thickened gallbladder wall: 2.3, 0.54 to 9.8, P=0.26; grit: 0.35, 0.10 to 1.2, P=0.09).

In 51% of the patients in our study, no thickened gallbladder wall or stone impaction was found. If these patients would have had no LC, the post-operative upper abdominal pain rate would fall from 25% to 12.5% (Table 1).

Discussion

This study showed that the presence of the sonographic signs of thickened gallbladder wall and/or stone impaction could be significantly related to relief of upper abdominal pain after cholecystectomy. Grit found on the pre-operative sonography of the gallbladder was significantly associated with persistence of upper abdominal pain.

We assumed that in patients with gallbladder stones the presence of sonographic signs like contracted gallbladder and sludge were signs of a diseased gallbladder and that therefore patients with these sonographic signs would be symptom free after cholecystectomy.

Since its introduction in 1989, laparoscopic cholecystectomy has become the preferred treatment of symptomatic gallbladder stones[2,4,5,7,10,14]. However, of all the patients who had a laparoscopic cholecystectomy, 12 to 47% had no relief of symptoms in a follow-up period of 24 to 120 months[3,6,12,17,18,23]. In this study the rate of persistence of upper abdominal pain was 25%.

Since the introduction of the LC, the number of cholecystectomies has increased by 30 to 55% in a period of 3 to 5 years[15,20]. Assuming that there is a constant number of patients with symptomatic gallbladder stones in the overall population and an increasing number of cholecystectomies, the absolute number of patients, who will not benefit from cholecystectomy will increase as well. This implies the quest for selection.

It seems useful to know in advance which patients are at risk for persistent symptoms, so patients can be better informed about the possible outcome of surgery. And even more important, in patients who have a low probability of symptom relief after LC, other diagnoses can be searched for.

In this study most patients had a sonography shortly after the onset of upper abdominal pain (median time 1 day). This seems preferable because a relation between symptoms and sonographic findings can be made. Several findings during gallbladder sonog-

raphy, like gallbladder wall thickening and stone impaction are probably reversible, and do not have to be present or are probably less prominent after some time.

In 51% of the patients in our study, no thickened gallbladder wall or stone impaction was found. If these patients would not have undergone LC, the upper abdominal pain rate in the operated group would fall from 25% to 12.5% (Table 1). In order not to miss symptomatic stones in this subgroup a strategy could be to repeat sonography during a new episode of upper abdominal pain.

This study confirmed the finding of our retrospective study that the presence of grit in the gallbladder on the preoperative sonography is related to the persistence of preoperative upper abdominal pain[23]. A possible explanation for this could be that, in these patients, grit is also present in the bile tree, which can give rise to recurrent complaints. In this study grit was present in 35% (23/65) of the patients. We assume that, although not proven in this study, these patients could benefit from LC combined with an additional procedure like papillotomy or papil dilatation.

In conclusion: This prospective study showed that sonographic signs of thickened gallbladder wall and/or impaction were associated with relief of upper abdominal pain after cholecystectomy. Grit found in the gallbladder on the preoperative sonography was associated with persistence of upper abdominal pain. Sonography appears therefore of value in the selection of patients with gallbladder stones for cholecystectomy.

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5

Are sonographic findings useful for the prediction of clinical outcome after cholecystectomy when pre-operative symptoms are taken into account?

Abstract

CONTEXT: *Despite many efforts to predict the outcome of surgical treatment in patients with gallstones, it remains difficult to tell which abdominal symptoms will improve after cholecystectomy. Sonographic findings may help in predicting clinical outcome.*
OBJECTIVE: *To evaluate the value of patient characteristics and pre-operative symptoms in the prediction of clinical outcome after laparoscopic cholecystectomy for gallstone disease. To evaluate the additional value of sonographic findings, such as thickness of the gallbladder wall, stone impaction and stone size.*
DESIGN: *A one-year, multi-center, follow-up study.*
SETTING: *The departments of surgery and radiology of nine hospitals in the area of Rotterdam, The Netherlands*
PATIENTS: *A total of 73 patients operated for gallstone disease.*
MAIN OUTCOME MEASURES: *Relief of upper abdominal pain and dyspepsia, one year after cholecystectomy.*
RESULTS: *The relief rates for upper abdominal pain and dyspepsia were 75% and 49% respectively. Older patients had higher relief rates for upper abdominal pain (adjusted odds ratio 1.06, 95% confidence interval 1.0 to 1.13). Flatulence, severe acid regurgitation and bloating were associated with persistence of upper abdominal pain, with adjusted odds ratios of: 6.25 (95% CI 0.9 to 50), (5.0 95% CI 1.16 to 20) and (7.1 95% CI 1.39 to 33.3), respectively. Flatulence, severe acid regurgitation and belching predicted the persistence of dyspepsia (adjusted odds ratios 5.5; 1.27 to 25, 5.9; 1.41 to 25 and 3.7; 1.05 to 12.5, respectively). The presence of grit in the gallbladder (0.3; 0.1 to 1.0), wall thickness ≥3 mm and/or stone impaction (4.0; 1.1 to 14.2) were each associated with upper abdominal pain relief but added little to the prognostic information of age and pre-operative symptoms (multivariable analysis).*
CONCLUSION: *Flatulence, severe acid regurgitation, bloating and belching predict the persistence of upper abdominal pain and dyspepsia in patients cholecystectomized for symptomatic gallbladder stones. Sonographic findings do not add significantly to the predictive value of age and pre-operative symptoms.*

The existence of gallstone-specific symptoms has been questioned[1,2]. The uncertainty around true clinical manifestations of gallstone disease is in sharp contrast with the unanimous recommendation that only symptomatic gallstones should be treated[3]. Although biliary pain defined as a severe, steady upper abdominal pain lasting more than 1 hour is related to gallstones[1,2,4,5], a causal relationship between other abdominal symptoms remains unclear. This makes it difficult to assess whether gallstones are truly symptomatic.

With the number of laparoscopic cholecystectomies increasing since the early 90s[6,7], several authors have felt the need grow to predict which patients will benefit from a cholecystectomy and which ones will not. Many efforts have been put in the prediction of the clinical outcome after cholecystectomy but the prognosis of individual patients undergoing this procedure is still a matter of debate[8-11]. Sonography provides more information than just the presence or absence of gallstones. Gallbladder size, wall thickness, stone impaction, and the size of the stones can all be recorded. In principle, these characteristics might be related to clinical outcome of cholecystectomy[9,13]. If so, they can be used to predict the likely outcome of surgery in individual patients. In that case sonography might help the clinician to decide if cholecystectomy will be beneficial to a patient. The probability of symptom relief, however, is a joint function of findings on sonography and other associated information on the patient[12]. The aim of the prospective study reported in this paper was to evaluate the additional value of sonography, beyond patient characteristics and pre-operative symptoms in predicting clinical outcome after cholecystectomy for gallstone disease.

Methods

Study Sample

Four hundred general practitioners (GPs) in the area of Rotterdam, the Netherlands, were invited to participate in the study, of which 247 (62%) accepted. All consecutive patients aged 18 years and older, who consulted a participating GP, between January 1996 and June 1998, with abdominal symptoms and in whom the GP considered the possibility of gallbladder stones, were eligible for the study. Patients who were suspected of acute cholecystitis or other acute abdominal illnesses were excluded.

Eligible patients were asked for written informed consent. In all patients, a standardised clinical examination was performed to determine abdominal tenderness, location of the pain, weight and length. Patients were then referred to a GP diagnostic service or to the radiology department of one of nine local hospitals for a standardised ultrasonographic examination of the upper abdomen. The research ethics committee of the University Hospital Rotterdam approved the study protocol.

Clinical Examination

We distributed a structured self-administered questionnaire to record the presence or absence of 13 abdominal symptoms during the last month. These symptoms were: nausea, vomiting, feeling of distension (bloating), belching, acid regurgitation, constipation, diarrhoea, flatulence, upper abdominal pain, upper abdominal pain after fatty food intake, upper abdominal pain lasting for more than one hour, jaundice, and fever ≥38°C. The severity of the symptoms was recorded on a 4-point scale: absent, mild, severe or very severe. Dyspepsia was defined as present whenever three or more dyspeptic symptoms (nausea, vomiting, bloating, belching, flatulence, and upper abdominal pain after fatty food intake) were quoted. Biliary pain was defined when the upper abdominal pain was severe and lasted more than one hour. One year after cholecystectomy a copy of the same questionnaire was sent by mail. Non-responders received a reminder by mail and a second reminder by telephone within one month.

Sonographic findings

Sonographic examinations were performed either by radiologists, senior radiological residents or experienced radiology technicians. All patients were examined in a fasting state with a 3.5 MHz scanner according to the following standardised protocol: Patients were placed in a supine position and on their left side. Whenever stone impaction was suspected, patients were placed in an upright position.

The following parameters were recorded: gallbladder size (normal, contracted or distended), wall thickness, number and size of stones, echogenic bile, and impaction of stones in the cystic duct or gallbladder neck. A contracted gallbladder was defined as a collapsed gallbladder filled with stones only. A gallbladder with a diameter of ≥4.5 cm was classified as distended. A gallbladder wall of ≥3 mm was classified as thickened and the presence of stones ≤3 mm were defined as grit. The diameter of the gallbladder was calculated as the maximum diameter perpendicular to the longitudinal axis. All items were scored on a structured form. Single sonographic findings and plausible combinations of two signs were analysed.

Statistical Analysis

Symptom relief rates, after cholecystectomy, were calculated for each symptom. The relief rate was defined as the number of patients in which the symptom had disappeared post-operatively, divided by the number of patients exhibiting the symptom pre-operatively. For each symptom the *de novo* rate was calculated as the number of patients who developed the symptom for the first time post-operatively divided by the number of patients without the symptom pre-operatively.

Associations were examined between age, sex, pre-operative abdominal symptoms, and sonographic findings versus post-cholecystectomy relief of upper abdominal pain, dyspepsia, and a symptom-free status. For this purpose the chi-square test statistic

with Yates correction was used. Postcholecystectomy upper abdominal pain included all reported upper abdominal pain independent of severity and duration, except upper abdominal pain that only occurred after fatty food intake.

Multivariable Modelling

All symptoms that were univariately associated with one of the three endpoints at a significance level of $P<0.25$ were entered into a multivariable logistic regression model. One model each was built for post-cholecystectomy relief of upper abdominal pain, dyspepsia, and a symptom-free status. These three outcome measures were the respective dependent variables. Initially significant patient characteristics and pre-operative symptoms ($P<0.25$) were entered in the model. Then sonographic findings were added, testing for a significant improvement in the prognostic regression model. The general likelihood ratio test statistic was used for this purpose, using the chi-square distribution and the number of additional variables added as the degrees of freedom, with a level of significance of $P \leq 0.05$.

For each of the dependent variables, adjusted (prognostic) odds ratios (OR) with asymptotic 95% confidence intervals were calculated from the regression coefficients. Deletion of cases with missing data may cause bias and will increase variance[15]. For 15 patients for whom one pre-operative clinical characteristic was missing and 6 patients for whom one post-operative finding was missing, the most cited answer was imputed. Patients for whom more than one value was missing were excluded from the multivariable analysis. SPSS software was used to perform the analyses[14].

Results

In total 233 patients were referred for ultrasonography of the upper abdomen. In this group 107 (46%) patients had gallbladder stones of whom 85 (79%) underwent cholecystectomy. Of these 73 (86%) patients responded to the follow-up questionnaire. The remaining 12 patients did not respond to the 2 reminders. They did not differ from the responding patients as far as age, sex, the presence of sonographic findings and time between sonography and cholecystectomy were concerned. The non-responders had more fever and diarrhoea than the responders did (75% versus 36%; $p=0.003$ and 67% versus 36%; $p=0.04$, respectively). The indication for cholecystectomy was upper abdominal pain in all 12 patients.

In sixty-five patients (89%) the indication for operation was upper abdominal pain. In 60 (92%) of these the pain occurred in episodes that lasted longer than 1 hour. In 45 (69%) upper abdominal pain was also provoked by fatty food intake. In 54 patients (83%) upper abdominal pain was accompanied by more than three dyspeptic symptoms. In only two patients the pain was not accompanied by dyspeptic symptoms.

Forty-four patients (60%) reported biliary pain, defined as an episode of severe upper abdominal pain lasting for more than one hour. In 40 (91%) of them biliary pain was

accompanied by dyspepsia.

A total of 61 (94%) patients suffered pre-operatively from dyspepsia. In 8 patients dyspeptic symptoms were the only indication for cholecystectomy.

After a median follow up of 14 months fifteen patients (21%) were completely symptom free. Sixteen patients (25%) still suffered from upper abdominal pain. In 12 of them (71%) upper abdominal pain was also provoked by fatty food intake; 16 patients (94%) suffered from more than 3 dyspeptic symptoms and 6 patients (35%) suffered from biliary pain. In total 41 patients had dyspeptic symptoms only; 7 of them (17%) had only upper abdominal pain after fatty food intake, and 16 patients (39%) reported more than three dyspeptic symptoms.

Table 1 shows the symptom relief rates and the *de novo* rates after cholecystectomy. Forty-nine of the patients with upper abdominal pain (75%) were relieved from their pain. In 31 (51%) of the patients with pre-operative dyspepsia the dyspeptic symptoms persisted. In total 24 (65%) of the patients with pre-operative acid regurgitation and 29 (62%) of the patients with pre-operative flatulence were not relieved of these symptoms after cholecystectomy.

Sonographic findings are presented in Table 2. The median time between the onset of abdominal symptoms and sonography was 1 day (1-15). In 63% of the patients the interval between sonography and surgery was less than one month, for 80% it was less than 2 months (range 0-405 days). Wall thickness ≥3 mm and stone impaction were associated with relief of upper abdominal pain, whereas grit was inversely related. Of the 8 patients without pre-operative upper abdominal pain, one patient had no sonographic findings, two had wall thickness ≥3 mm and stone impaction, one had a contracted gallbladder and stone impaction. All others either had wall thickening (2), stone impaction (1) or grit (1). One patient with stone impaction was completely symptom free after cholecystectomy.

Table 3 summarises the findings on the prognostic value of pre-operative findings for post-operative symptom relief. In the univariate analysis higher age, a wall thickness ≥3 mm and/or stone impaction on sonography were significantly associated with post-operative relief of upper abdominal pain (odds ratio >1). Flatulence, severe bloating, severe acid regurgitation and a stone diameter ≤3 mm (grit) on sonography, predicted the persistence of upper abdominal pain (odds ratio <1). None of the other symptoms tested showed a significant relation (P≥0.25) with upper abdominal pain relief. Comparable results were found for the post-operative relief of dyspepsia. Flatulence, severe acid regurgitation and severe belching were associated with persistence of dyspepsia, whereas the finding of echogenic bile on sonography predicted relief of dyspepsia.

In the multivariable analysis the sonographic findings did not add significantly to the predictive value of the abdominal symptoms (chi-square statistics 5.2, 2 df, $p>0.05$ for relief of upper abdominal pain and 2.6, 1 df, $p>0.5$ for relief of dyspepsia).

Table 4 presents the distribution of the abdominal symptoms, their association with symptom relief, the predicted symptom relief rates as calculated from the logistic regression model, and the observed symptom relief rates. In those patients with a high-calculated probability of symptom relief, most patients also have a thickened gallbladder wall

Table 1
Relief rates, persistence, and *de novo* rates of symptoms after cholecystectomy (n=73)

	Frequency pre-operative	Symptom relief n (%)	No relief n (%)	*De novo* n (%)
Biliary pain	44/73	38 (86)	6 (14)	0
Upper abdominal pain	65/73	49 (75)	16 (25)	1 (13)
Dyspepsia	61/73	30 (49)	31 (51)	1 (8)
Belching	56/72	24 (43)	32 (57)	2 (13)
A feeling of distension (bloating)	56/72	33 (59)	23 (41)	5 (31)
Upper abdominal pain after fatty food intake	46/73	32 (70)	14 (30)	5 (19)
Nausea	58/70	39 (67)	19 (33)	2 (17)
Flatulence	47/73	18 (38)	29 (62)	10 (39)
Vomiting	39/71	35 (90)	4 (10)	4 (13)
Acid regurgitation	37/73	13 (35)	24 (65)	6 (17)
Diarrhoea	26/73	6 (23)	20 (77)	12 (26)
Constipation	29/72	19 (66)	10 (34)	5 (12)

Table 2
Pre-operative sonographic findings in patients with gallstones (N=73) and their association with post-operative symptom relief

	Pre-operative Sonographic findings N=73 (%)	Odds Ratio for relief of upper abdominal pain (N=65) (95% confidence interval)	Odds Ratio for relief of dyspepsia (N=61) (95% confidence interval)
Gallbladder size:			
Normal (<4.5 cm)	57 (78)	1	1
Contracted*	8 (11)	0.5 (0.1 to 2.3)	0.8 (0.2 to 3.9)
Distended (≥ 4.5 cm)*	8 (11)	§	1.4 (0.3 to 6.9)
Thickness of wall ≥3 mm	27 (37)	**3.0 (0.8 to 11.9)**	0.7 (0.2 to 2.0)
Diameter of stones ≤ 3 mm (grit)	25 (34)	**0.3 (0.1 to 1.0)**	1.2 (0.4 to 3.5)
Echogenic bile	13 (18)	1.8 (0.4 to 9.2)	**4.0 (1.0 to 16.6)**
Stone impaction	24 (33)	**4.1 (0.8 to 20.0)**	0.8 (0.3 to 2.3)
Thickness of wall ≥ 3mm and/or stone impaction	32 (44)	**4.0 (1.1 to 14.2)**	1.1 (0.4 to 2.9)

*A normal gallbladder size was taken as the reference category
§ one cell was empty; no proper estimate of the odds ratio could be made.
Bold: P<0.25

Table 3
Prediction of outcome after cholecystectomy by pre-operative symptoms and sonographic findings, a multivariable analysis

	Crude Odds Ratio (95% C.I.)	Multivariable Odds Ratio, without sonographic findings (95% C.I.)	Multivariable Odds Ratios, including sonographic findings (95% C.I.)
Relief of upper abdominal pain (N=65)			
Age	1.05 (1 to 1.10)	1.06 (1 to 1.13)	1.04 (0.97 to 1.10)
Flatulence (yes/no)	0.18 (0.04 to 0.86)	0.16 (0.02 to 1.10)	0.21 (0.03 to 1.60)
Acid regurgitation (no, mild / severe, very severe)	0.12 (0.03 to 0.42)	0.20 (0.05 to 0.86)	0.11 (0.02 to 0.66)
Bloating (no, mild / severe, very severe)	0.12 (0.03 to 0.46)	0.14 (0.03 to 0.72)	0.13 (0.02 to 0.82)
Diameter of stones ≤ 3mm (grit)	0.31 (0.10 to 0.99)		0.25 (0.04 to 1.48)
Stone impaction (yes/no) and/or wall thickness ≥ 3mm	4.0 (1.13 to 14.2)		4.0 (0.70 to 23.7)
Relief of dyspepsia (N=61)			
Flatulence (yes/no)	0.26 (0.07 to 0.93)	0.18 (0.04 to 0.79)	0.21 (0.05 to 0.97)
Acid regurgitation (no, mild / severe, very severe)	0.19 (0.05 to 0.66)	0.17 (0.04 to 0.71)	0.19 (0.04 to 0.78)
Belching (no, mild / severe, very severe)	0.31 (0.10 to 0.95)	0.27 (0.08 to 0.95)	0.21 (0.06 to 0.80)
Echogenic bile (yes/no)	4.0 (0.96 to 16.6)		3.9 (0.71 to 20.85)
Symptom free (N=73)			
Flatulence (yes/no)	0.19 (0.06 to 0.64)	0.23 (0.06 to 0.89)	
Dyspepsia	0.28 (0.07 to 1.04)	0.66 (0.14 to 3.08)	

95% C.I. = 95% confidence interval

and/or stone impaction. In those patients with a low predicted relief rate for abdominal pain only few patients have these sonographic findings, but the patients in whom sonographic signs are found show higher symptom relief rates (70% (7 of 10) as opposed to 33% (6 of 18) in patients without sonographic findings). Echogenic bile did not add to the predictive value for relief of dyspepsia of the abdominal symptoms.

Discussion

In a follow-up study of cholecystectomized patients, the prognostic value of patient's characteristics, pre-operative abdominal symptoms and findings on sonography for post-operative symptom relief were evaluated. Older patients had higher relief rates for upper abdominal pain. Flatulence, severe acid regurgitation, bloating and belching were associ-

Table 4
Predictive value of pre-operative symptoms on symptom relief and the additional value of sonographic findings

	N	Predicted probability of symptom relief (range based on age differences)	Observed probability of symptom relief	Symptom relief in patients with negative sonographic finding: wall thickness < 3 mm, no stone impaction	Symptom relief in patients with positive sonographic finding: wall thickness ≥ 3 mm and/or stone impaction
Relief of upper abdominal pain (N=65)					
No flatulence, acid regurgitation or bloating	15	0.99 (0.97 to 1)	1.0	5/5	10/10
Flatulence	16	0.94 (0.83 to 0.99)	0.94	7/7	8/9
Acid regurgitation	1	0.99	1.0	1/1	-
Bloating	5	0.92 (0.83 to 0.98)	1.0	2/2	3/3
Flatulence and acid regurgitation	4	0.57 (0.38 to 0.83)		2/4	-
Flatulence and bloating	11	0.59 (0.36 to 0.88)	0.55	3/8	3/3
Acid regurgitation and bloating	3	0.55 (0.47 to 0.65)	0.33	-	1/3
Flatulence, acid regurgitation and bloating	10	0.31 (0.11 to 0.52)	0.40	1/6	3/4
Total	65		0.75	21/33	28/32
				Echogenic bile (no)	Echogenic bile (yes)
Relief of dyspepsia (N=60)					
No symptoms	4	0.93	1.0	3/3	1/1
Flatulence	12	0.70	0.67	7/11	1/1
Acid regurgitation	1	0.69	1.0	1/1	-
Belching	7	0.78	0.71	2/4	3/3
Flatulence and acid regurgitation	4	0.29	0.25	1/4	-
Flatulence and belching	19	0.39	0.42	5/10	3/9
Acid regurgitation and belching	3	0.38	0.33	1/2	0/1
Flatulence, acid regurgitation and belching	10	0.10	0.10	1/9	0/1
Total	60		0.48	21/44	8/16

ated with persistence of upper abdominal pain and dyspepsia. Sonographic findings did not add significantly to the prognostic value of pre-operative characteristics, when the latter had been incorporated into a logistic prediction model. In patients with a low likeli-

hood of upper abdominal pain relief, wall thickness ≥3 mm or stone impaction were associated with higher relief rates for upper abdominal pain. This association did not reach statistical significance.

Biliary pain defined as a steady severe pain in the upper abdomen lasting ≥1 hour is suggested to be causally related to gallstone disease. In our study the relief rate for biliary pain was high (86%). In total 14 out of 44 patients (32%) with pre-operative biliary pain still had upper abdominal pain 14 months after cholecystectomy. This finding indicates that biliary pain is not specifically caused by gallstones and that the indication for cholecystectomy should not solely be based on the presence of biliary pain.

Patients with flatulence and severe acid regurgitation and bloating or belching had low calculated relief rates. In these patients a finding of stone impaction or a thickened gallbladder wall at sonography increased the probability of symptom relief. As numbers were small, such an association could not reach statistical significance and larger patient groups are required to further explore this subgroup relation.

The variability in symptom relief rates as reported by others can be explained by differences in the methods for evaluation used, wording of questionnaires, varying duration of follow-up, patient case mix and differences in the strategies used for the analysis (symptom frequencies or symptom relief rates)[16]. Only few studies have performed a multivariable analysis. Gui *et al.*[9] found fatty food intolerance, normal bowel habits, a body mass index <26 kg/m2, and a thick-walled gallbladder to be predictive for a symptom free outcome after operation. A clinical relevant discrimination between patients with and without symptoms after cholecystectomy could not be reached however. Only 15 patients in our sample were completely symptom-free at follow-up. Patients without preoperative flatulence or dyspepsia were more frequently free of symptoms at follow-up. Sonographic findings did not have additional prognostic value. Ure *et al.*[10] could not differentiate between patients with and without complaints after operation. Their model included 8 symptoms, age, sex and weight loss. Luman *et al.*[11] found bloating, constipation and the use of psychiatric medication to be predictive of persisting complaints after operation. We confirmed that bloating was predictive for the persistence of symptoms. A relation between psychic vulnerability and persisting abdominal pain after cholecystectomy was also reported by Jørgenson *et al.*[17] but could not be evaluated in our study. The Mulgo group reported that in a prospective study patients with abdominal pain 1 year after cholecystectomy were characterised by the preoperative presence of dyspeptic symptoms, 'irritating abdominal pain', and an introverted personality and by the absence of 'agonising' pain and symptoms coinciding with pain[18]. In our study the severity of the pain was not related to a pain free outcome after cholecystectomy. The finding of dyspeptic symptoms predicting postoperative abdominal pain was confirmed in our study sample.

In a study on the diagnostic value of gastrointestinal symptoms for gallstones on ultrasound Farrell *et al.*[19] reported that pain lasting for more than 1 hour, any radiating pain and the absence of flatulence were independent predictors of gallstones. This finding is in accordance with our finding that flatulence predicts the post-operative persistence of

symptoms.

The influence of age on outcome of cholecystectomy was previously reported by Mort *et al.*[20]. After adjustment for other patient characteristics, indication for operation, and co-morbid conditions, older patients (≥60 years) experienced more symptomatic relief than did younger patients. A possible explanation is that older patients (and physicians?) may be more risk averse than younger patients and more likely to refuse surgery when offered, particularly when the likelihood of symptomatic relief is uncertain.

Pre-operative findings in patients with gallstones allow the clinician to discriminate between patients with high and low relief rates for upper abdominal pain. With our multivariable model 57% of the patients (37 of 65) had a predicted probability for upper abdominal pain relief of more than 90%, the remaining 43% (28 of 65) had a probability of <60%. The question remains whether in case of such an almost fifty-fifty chance of symptom relief an operation is indicated. Based on our study, sonographic signs like gallbladder wall-thickening and stone impaction were not able to add further statistically significant prognostic information that would allow a distinction between patients who will benefit from cholecystectomy and those who will not. Further studies with higher power should explore the association between sonographic findings with symptom relief in specific subgroups. To evaluate which symptoms actually improve due to the cholecystectomy a randomised controlled trial remains a necessity.

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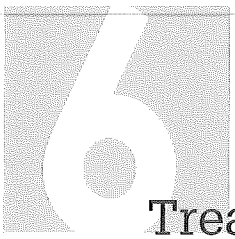

Treatment of gallstones in patients with abdominal symptoms

A decision analysis comparing laparoscopic cholecystectomy with expectant management

The main reasons for treatment of symptomatic gallstones are permanent relief of abdominal symptoms, including pain and the prevention of biliary complications and death.

Natural history data indicate that after an episode of biliary pain, the probability of having at least one more episode of pain over the next years is about 40-50%[1,2] with a decreasing rate in the years thereafter. Several studies indicate that the annual rate to develop a biliary complication is 1-2% and that the rate remains steady for many years[1,2,3].

All surgical procedures are accompanied with inconvenience and the risk of complications and death. For some patients the likelihood of symptom relief after cholecystectomy does not outweigh the downsides of surgery. These patients rather avoid surgical therapy.

In a quantitative analysis Ransohoff and Gracie[4] compared a strategy of immediate open cholecystectomy with a strategy of expectant management until a complication occurs. The outcome of the treatment strategies for a 30-year old man with gallstones after a period of biliary pain was measured in terms of life expectancy. Choosing expectant management a 30-year old man had a cumulative lifetime risk of death related to gallstone disease of 2%, choosing cholecystectomy this risk was 0.1%. Because these deaths almost all occurred at older ages the loss of life expectancy, choosing expectant management was only slightly increased (up to two months).

Elective cholecystectomy is a relatively safe, surgical procedure performed under total anaesthesia, which definitively eradicates gallstones and the subsequent risk of biliary complications in the vast majority of patients.

In 1989 laparoscopic cholecystectomy was introduced. As a surgical intervention with less inconvenience compared to open cholecystectomy this therapy received great enthusiasm from clinical practitioners. However the rate of complications like common bile duct injury, bile leaks and bowel injury tends to be higher then for open cholecystectomy.

In a cost-effectiveness study of laparoscopic cholecystectomy versus open cholecystectomy Bass *et al.*[5] evaluated the effectiveness of both procedures in terms of total mortality and quality adjusted survival. They concluded that laparoscopic cholecystectomy is likely to be less costly and more effective than open cholecystectomy for most patients, as long as it does not routinely require preoperative cholangiography and is not associated with increased professional fees or increased risks of retained stones or bile duct injury. At the moment laparoscopic cholecystectomy is the first choice treatment for symptomatic gallstones.

If a patient's primary goal is to avoid further pain episodes, prompt intervention may be chosen. A very important assumption to be made here is that the intervention is effective and that relief of pain will be established after intervention. This assumption is difficult to hold after an analysis of the relief rates of abdominal symptoms after cholecystectomy[7]. In 14% of patients biliary pain persisted after operation and of the patients relieved from biliary pain 32% still had mild upper abdominal pain. Furthermore, 40-80% of patients with gallstones was referred for cholecystectomy because of symptoms other than biliary pain[6,7]. The relief rates for these symptoms - think of bloating, simple upper abdominal pain and fatty food intolerance - were even less favourable than those for bil-

iary pain.

The decision which therapy fits best to the individual patient with symptomatic gallstones is complex if one realises that the pros and cons of the two strategies are differently distributed over time. Furthermore the utility of therapy should not only be measured as the average duration of life but in particular as the average time of life spent without abdominal symptoms.

This paper presents a decision analysis which was set up to assess quantitatively the risks of a surgical strategy and management based on 'watchful waiting', and to quantify the difference between these strategies in long-term symptom-free status in a patient with gallbladder stones after an episode of biliary pain.

Material and Methods

Treatment with laparoscopic cholecystectomy is nowadays available for almost all of the patients with gallstones. The techniques of formal decision analysis were used in an attempt to make explicit the risks and benefits of the different management strategies for men and women at different ages, with a history of one or more periods of abdominal symptoms thought to be caused by gallbladder stones, found after a sonographic examination of the abdomen. The patients had no previous gallbladder surgery.

Structure of the decision problem

In a Markov model we compared two therapeutic options: elective laparoscopic cholecystectomy and expectant management (watchful waiting). To establish the relative effect of these options we assessed life expectancy and the expected time spent in two different health states: a state with the abdominal symptoms related to gallstones, and one without symptoms. Figure 1 contains a graphical representation of the decision model that was used in the analysis.

If elective laparoscopic cholecystectomy is chosen the first consequence is operative death (dead). During laparoscopy emerging complications may require an open procedure or an exploration of the common bile duct. Once the patient survives surgery this patient will be either free of pain (well) or with the same symptoms as before operation (abdominal symptoms). The patient will remain in one of these conditions for the rest of his/her life until retained stones lead to an intervention or until the patient dies from causes not related to gallstone disease (dead). After this intervention the patient may either be free of abdominal symptoms (well) or suffer from persisting symptoms (abdominal symptoms) for the rest of his/her life.

If expectant management is chosen the patient may die from other causes (dead), suffer from abdominal symptoms related to gallstones or develop a biliary complication, requiring acute cholecystectomy either with or without common bile duct exploration. After these interventions the patient may either be free of abdominal symptoms (well) or suffer from persisting symptoms (abdominal symptoms) for the rest of his/her life. If no

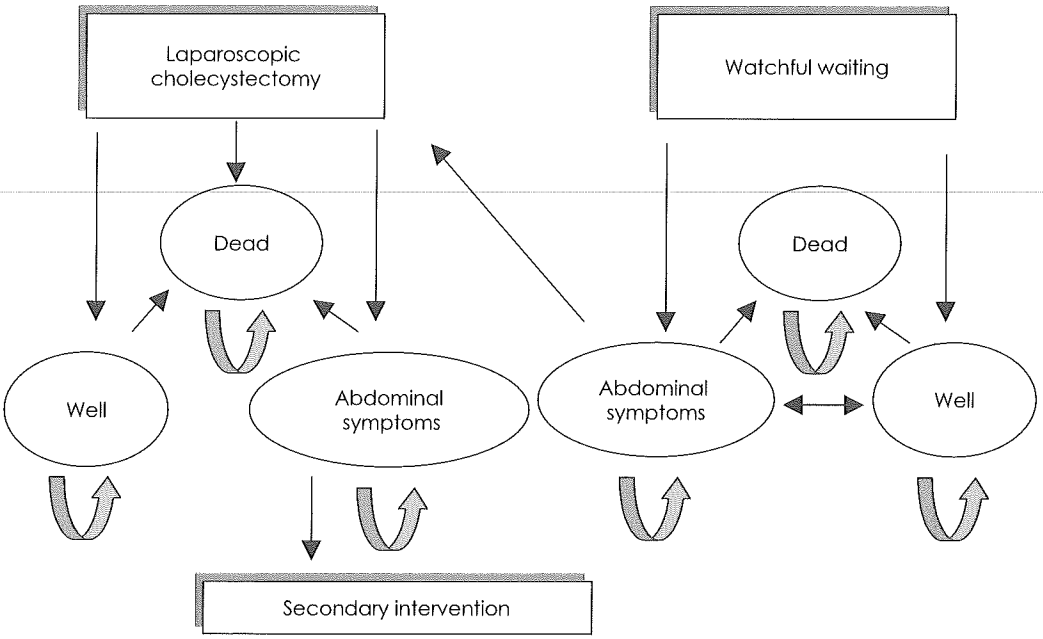

Figure 1
Choices of management for gallbladder stones and their consequences.

abdominal symptoms occur the patient will be in a stable pain-free condition (well). The change of health-states continue for each patient until the patient dies.

The probabilities used in this model are summarised in Table 1. In patients with untreated symptomatic gallstones the annual incidence of recurrent symptoms is reported to decline from 0.38 in the first year to 0.17 in the years thereafter[1]. Others report an almost constant annual incidence of 0.52 in the first year and 0.44 after 25 years of follow-up[2]. In this analysis a constant rate of 0.38 and a constant rate of 0.17 are analysed.

The annual incidence of emergency surgery for biliary complications declines from 0.083 in the first year to 0.01 after 25 years of follow-up[3]. Others have reported this rate to remain almost constant at a lower level of 0.01 to 0.016[2]. The trend of an early high rate of complications in part of the patients followed by a constant incidence suggests two different populations of patients. A first group of patients who develop a complication within a short time period and will be operated for that reason and a second group who develop complications at a much lower rate. In this analysis a constant rate of 0.016 has been used.

The operative mortality rates depend on age, sex and whether the operation is elective or acute. For a forty-year-old women operative mortality rates are estimated to be 0.007% without and 0.06% with common bile duct exploration, after elective laparoscopic cholecystectomy. For an eighty-year-old woman these operative mortality rates increase to 0.08% and 7.6% respectively. Both mortality rates are about four times higher after an

Table 1
Estimates of probabilities used in the decision analysis with their literature references

	Reported range	References	Probabilities used in this analysis
Expectant management			
Annual rate of abdominal symptoms and biliary pain	0.17 to 0.52	1,2	0.17 and 0.38
Annual rate of biliary complications	0.01 to 0.083	2,3	0.016
Annual rate of gallbladder cancer after the age of 50 years	0.0001 to 0.0007	4,48,49	0.0001 and 0.0007
Laparoscopic cholecystectomy			
Conversion to open cholecystectomy			
In elective cholecystectomies	0.03 to 0.10	11,24,26,44,46,47	0.15; 0-1
In acute cholecystectomies	0.16 to 0.44	8,44,45	
Common bile duct exploration (including bile duct injury) given conversion to open cholecystectomy	0.09 to 0.20	9,44,46	0.15
Secondary intervention due to retained stone in bile duct	0.004 to 0.012	26,44	0.012
Post-operative rate of symptom persistence	0.05 to >0.50	7	0.05; 0-1
Death of other causes		Dutch life tables	
Operative mortality		10 - 45	Fig.2

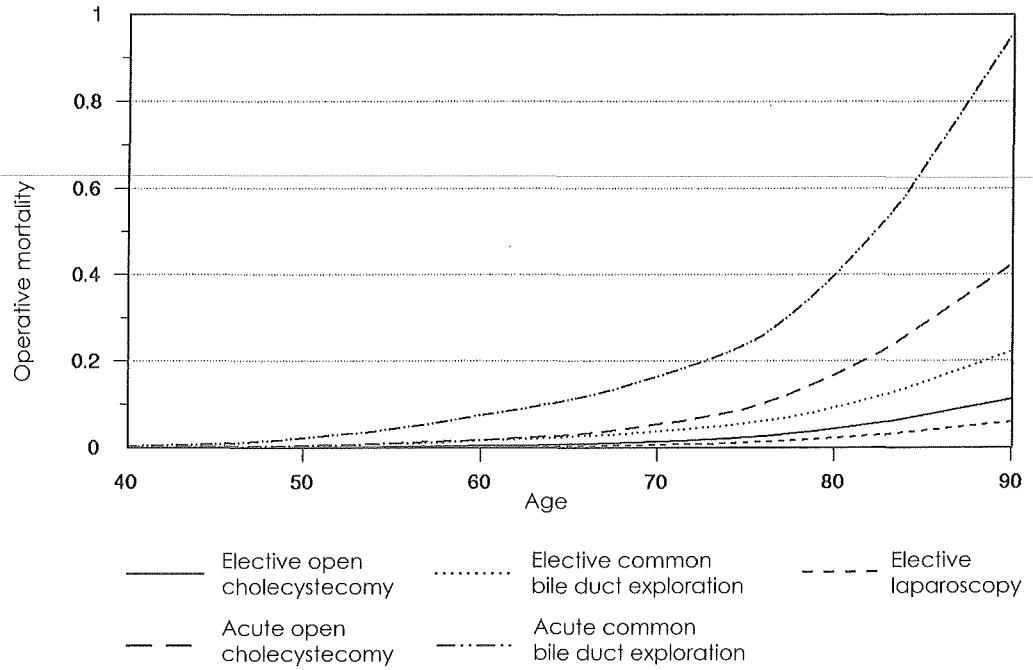

Figure 2
Extrapolation of estimates reported in the literature of operative mortality rates, related to different surgical interventions for gallstone disease.

acute cholecystectomy due to gallstone complications. These estimates are based upon a review of studies published after 1980[10-46]. Mortality related to a surgical intervention for gallstones is low. However, mortality increases rapidly after age 75. The mortality rates at older ages represent the effect of age as well as the effect of co-morbidity (Fig. 2). A healthy eighty-year-old woman will probably have lower operative mortality risks as estimated here.

The long-term symptom-free status provided by cholecystectomy was evaluated in very few studies. Most studies have a follow-up of 1-2 years. Reported rates of postoperative abdominal symptoms vary between 5% and more than 50%[7]. In this analysis the effect of varying rates of postoperative symptoms will be evaluated.

Some laparoscopic cholecystectomies will have to convert to an open procedure. This rate depends upon the indication for operation. In acute procedures conversion rates of 30%[8] to 44%[43] are reported. Nine to twenty percent[9,44,46] of conversions are due to the necessity of bile duct exploration or injury of a bile duct (0.3%[9] to 0.5%[46]). Reported rates of conversion to open cholecystectomy after elective cholecystectomy vary between 3%[44] and 10%[47].

One percent of the patients treated with cholecystectomy requires a secondary intervention for retained stones[26,44].

Studies on the incidence of gallbladder cancer suggest an increased risk in patients

with abdominal symptoms and gallbladder stones compared to patients with asymptomatic stones. Gallbladder cancer becomes manifest at ages above 50 years and is a fatal disease. The risk of gallbladder cancer is low according to currently available evidence but there is some disagreement about the rates in subgroups of patients. The Pima-Indians may be considered such a high-risk group. Whether persons of other races might fall into this category is an unresolved question but may include patients with a calcified gallbladder. In this analysis we considered a lifetime risk for gallbladder cancer in a 30-year-old person to be 1.4%, that is a constant yearly rate of 0.0007 after the age of 50 years[48]. The rate under the age of 50 years was considered to be zero. This risk estimate is comparable to the risk for gallbladder cancer as estimated by Ransohoff[49] (Lifetime risk in a 30 year-old person of 1.7%, above 50 years: annual risk of 0.0008). This estimate is relatively high compared to estimates of the risk of gallbladder cancer used in earlier studies[4] (above 50 years: annual risk 0.0002). Both estimates are evaluated in this analysis. We used a discount of 5% in the model for the life expectancy over time. Discounting is used to reflect that a year of life lost immediately is valued more highly than the same year of life lost in the future.

Assumptions made in this analysis

General

- Death related to gallstone disease is either due to operative mortality or gallbladder cancer. No deaths occur due to other events such as biliary pain.
- In a person who survives cholecystectomy, life expectancy is not decreased compared with that of the general population.

In favour of non-surgical procedures

- The biliary complications considered in this analysis are those requiring acute cholecystectomy.
- Conversion to open surgery during laparoscopic cholecystectomy will have an operative mortality and morbidity risk comparable to acute biliary surgery.
- The annual incidence of recurrent abdominal symptoms does not differ from the incidence of biliary pain.

The model was analysed for both sexes, various ages, two estimates of the risk for gallbladder cancer and two estimates for the annual rate of biliary pain. A sensitivity analysis was performed to detect a threshold for the rate of postoperative persistence of symptoms and the rate of conversion to open cholecystectomy.

Results

A choice for elective laparoscopic cholecystectomy yields greater life expectancy and more time spent without biliary pain regardless of the age at surgery (Table 2). The gain in life expectancy is 251 days choosing laparoscopic cholecystectomy in women at age 30 and decreases to a gain of 136 days in women at age 70. Choosing laparoscopic cholecystectomy the gain in life expectancy depended on the probability of conversion to open cholecystectomy. In a 70-year-old woman life expectancy was equal for both strategies at a conversion rate of 0.44, for a 70-year-old man this threshold was reached at a conversion rate of 0.28. In younger patients laparoscopic cholecystectomy remained the preferred strategy regardless of the risk for conversion.

The lifetime cumulative incidence of biliary complications requiring an acute cholecystectomy is 50% in a 40-year-old person.

Figure 3
The post-operative symptom persitence rate at which level both management strategies will give the same years of time spent without abdominal symptoms. If the actual post-operative rate of symptom persistence lies above the indicated level than expectant management is to be preferred above laparoscopic cholecystectomy. If the actual post-operative rate of symptom persistence lies below the indicated level than laparoscopic cholecystectomy is to be preferred above expectant management. (Annual risk of gallbladder cancer: 0.0007.)

♦ : annual risk of abdominal symptoms choosing expectant management 0.38
□ : annual risk of abdominal symptoms choosing expectant management 0.17

Table 2
Projected loss of life expectancy and time spent without biliary pain due to expectant management versus elective laparoscopic cholecystectomy

Age when gallstones were discovered	Annual rate of biliary pain 0.38				Annual rate of biliary pain 0.17		
	Life expectancy after laparoscopy (years)	Life expectancy Above 50 years: annual gallbladder cancer risk 0.0002 (loss in days)	Life expectancy Above 50 years: annual gallbladder cancer risk 0.0007 (loss in days)	Years spent without symptoms (loss in years)	Life expectancy Above 50 years: annual gallbladder cancer risk 0.0002 (loss in days)	Life expectancy Above 50 years: annual gallbladder cancer risk 0.0007 (loss in days)	Years spent without symptoms (loss in years)
Women							
30	50.6	140	251	10.7	124	235	8.2
40	40.9	141	253	8.8	125	238	6.7
70	14.5	76	136	3.5	56	116	2.7
Men							
30	44.4	63	142	9.4	55	135	7.1
40	34.9	63	144	7.5	55	136	5.7
70	10.9	19	62	2.7	8	51	2.0

Biliary pain defined as a steady, severe upper abdominal pain lasting more than 1 hour, is considered to be related to gallstone disease. The difference in time spent without biliary pain is considerable ranging from 10.7 years in women at age 30 to 3.5 years in women at age 70.

Forty to eighty percent of patients with gallstones present with other abdominal symptoms than biliary pain. The utility of therapy measured as the average duration of time spent without abdominal symptoms depended on the rate of persisting symptoms after cholecystectomy (Fig. 3). For both sexes expectant management will render more symptom-free years, if postoperative symptom persistence rates will be more than 20-30%.

Patients at low risk for gallbladder cancer will gain less life expectancy by choosing immediate laparoscopic cholecystectomy. For 70-year-old patients the difference in life expectancy is reduced to a few days (Table 2).

Discussion

As therapy for gallstones has become safer and easier to perform it has become increasingly attractive to consider treating persons with gallstones. In making decisions about treatment clinicians and patients should be guided considering that management strategies can be aimed at two distinct goals: to prevent symptoms related to gallstones, or to prevent a biliary complication or death.

To prevent a biliary complication or death immediate laparoscopic cholecystectomy was found to be the preferred strategy for both sexes at all ages. The average amount of life expectancy gained by immediate laparoscopic cholecystectomy ranged from 51 to 253 days (Table 2). In addition to reducing mortality it also helps to avoid an urgent operation which would eventually be needed in about 50% of patients who might develop a biliary complication like acute cholecystitis. This finding was comparable to the findings of Ransohoff[49].

In terms of life expectancy laparoscopic cholecystectomy should be avoided in older persons with a high conversion risk. A 70-year-old man with a probability greater than 0.28 for conversion to open cholecystectomy would gain life expectancy by choosing expectant management. The conversion rates depend on a range of different factors: experience of the surgeon and indication for operation (acute cholecystitis). Based on sonographic findings conversion may be predicted. In a prospective study of patients who underwent an elective laparoscopic cholecystectomy patients with a distended gallbladder of ≥4.5 cm on sonography showed a conversion of laparoscopic to open cholecystectomy in 29% as opposed to 6% in patients without a distended gallbladder[47].

The gain of choosing laparoscopic cholecystectomy more then halved with the lower estimates of the risk for gallbladder cancer. Estimates of the risk for gallbladder cancer vary. Further research in risk factors for gallbladder cancer is needed[49].

To prevent biliary pain the gain in time spent without biliary pain by choosing laparo-

scopic cholecystectomy was considerable. This gain ranged from 10.7 years in women at age 30 to 2 years in men at age 70, all in favour of laparoscopic cholecystectomy (Table 2). Forty to eighty percent of patients who undergo cholecystectomy, however, do not present with biliary pain. Whereas the reported post-operative relief rate for biliary pain is high, 95%, relief rates for other abdominal symptoms mostly accompanying upper abdominal pain are less favourable and range from 23-70%[7]. The preferred choice of treatment depended on the probability of post-operative abdominal symptom persistence. A probability of more then 30% for abdominal symptoms persisting after cholecystectomy would favour expectant management in all patients. In terms of time spent without symptoms it is important to be able to predict the risk of post-operative persistence of symptoms. Single pre-operative symptoms are shown to have little prognostic value[7]. It is the clinical complex of symptoms and signs that may predict outcome after cholecystectomy. In a prospective study of patients who underwent an elective laparoscopic cholecystectomy we found that any combination of flatulence, severe acid regurgitation, and bloating was associated with the persistence of upper abdominal pain in 54% as opposed to a persistence of 3% in all other patients[50]. These percentages are well above and respectively, below the threshold for postoperative symptom persistence that determines the decision whether to operate or to wait.

One may consider a patient with no relief of symptoms after cholecystectomy as a patient with asymptomatic gallbladder stones and abdominal symptoms due to other causes. Such patients may have lower - but yet unknown - biliary complication rates as used in this analysis. Therefore, the loss in life expectancy, choosing expectant management, may be much smaller as calculated in this study. It is unclear if these patients are comparable to the asymptomatic patients with gallbladder stones in which Ransohoff in a decision analysis preferred expectant management[49].

Conclusion

In patients with biliary pain, defined as a severe steady upper abdominal pain lasting more then one hour, not accompanied by other abdominal symptoms, elective laparoscopic cholecystectomy is the preferred treatment in terms of life expectancy and years spent without biliary pain.

In patients with gallstones and abdominal symptoms other than single biliary pain, the option of expectant management should be considered in patients with low symptom relief rates after cholecystectomy and in older men with a high risk for conversion to open cholecystectomy. The prevention of recurrence of abdominal symptoms, including pain and the prevention of the occurrence of biliary complications and death has to be valued by the patient. The clinician has to inform the patient about the likelihood of post-operative persistence of symptoms and the risk of conversion from laparoscopic to open cholecystectomy. The patient needs to become informed about the consequences of the choice of management in terms of life expectancy and time spent without symptoms.

Most studies evaluating the post-operative outcome of cholecystectomy are uncon-

trolled. Firm estimates of post-operative outcome can only be reached by performing randomised trials. Further research is needed to gain information about the risk of conversion from laparoscopic to open cholecystectomy, biliary complication rates in patients with a diversity of abdominal symptoms and gallbladder stones, and risk-factors for gallbladder cancer.

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Summary

The aim of this thesis was to identify abdominal symptoms closely associated with gallstone disease, in order to evaluate whether these symptoms could predict symptomatic outcome after cholecystectomy.

The first objective was to evaluate the association between abdominal symptoms and the presence of gallbladder stones. **Chapter 1** presents the results of a systematic review of studies evaluating the diagnostic accuracy of abdominal symptoms for gallstones. Biliary pain, defined as a steady, severe upper abdominal pain lasting for more than 1 hour, was the only symptom that was consistently and statistically significant related to the presence of gallstones. A statistically significant difference was also found between the diagnostic value of biliary pain in screening studies of the general population compared to the diagnostic value of biliary pain in studies of patients referred for radiodiagnostic examination of the gallbladder. This finding was confirmed in a recent study of Thijs *et al.* who found no relation between biliary pain and gallstones in a screening situation but a significant association in a study of patients referred for radiodiagnostic examination of the gallbladder. Symptoms in a screening population may be milder than in the clinical setting due to less extended gallstone disease. Alternatively, symptoms may be so rare that the statistical power to detect an association is low. The first explanation for our finding was confirmed by the fact that the relation between biliary pain and gallstones became stronger according to the extent of gallstone disease in the patients studied. In seriously ill patients an OR of 4.1 (95% CI 2.8 to 6.1) was found. In all other patients the discriminative capacity of biliary pain remained clinically irrelevant.

An association between food- or fat intolerance and the presence of gallstones had

to be excluded. This conclusion was not in accordance with the conclusion of Thijs *et al.* who stated that the relation between food intolerance and gallstones remained controversial. They based their conclusion on a high pooled odds ratio (OR 14.0, 95% CI 9.13 to 21.7) found in an earlier meta-analysis[2]. In a further discussion with the authors we could demonstrate that this OR was erroneously based on the misinterpretation of the data of one particular study (see Appendix, p. 93).

In daily practice clinicians will not base their diagnosis on single, separate symptoms but rather on the complex of symptoms and signs. Our second objective was to identify a combination of abdominal symptoms closely associated to the presence of gallbladder stones. In **chapter 2** the results of a follow-up study of patients suspected for gallstones were presented. The association between biliary pain and gallstones was confirmed in this study. Biliary pain, vomiting and jaundice were found to be the abdominal symptoms independently related to gallstones. These symptoms could not be used to separate patients with from those without gallstones. We hypothesised that vomiting is only related to gallstones in seriously ill patients and should be regarded as a gastrointestinal symptom accompanying severe upper abdominal pain in gallstone disease.

Based on these two studies we concluded that the decision as to whether or not a patient's symptoms are attributable to gallstones couldn't be based on the specificity of these symptoms for gallstones found on sonography.

In **chapter 3** the objective was to identify abdominal symptoms that are likely to disappear after cholecystectomy in patients with gallstones. This chapter contains the results of a systematic review of studies evaluating relief of abdominal symptoms after cholecystectomy and the results of a follow-up study of patients suspected for gallstones by their GP. Almost all patients (±90-95%) with pre-operative biliary pain experienced pain relief after cholecystectomy. This high relief rate, however, was not specific for cholecystectomized patients. Patients without gallstones presenting with 'biliary pain' at their GP also showed high relief rates (80%) after ± one-year follow-up. The relief rates of upper abdominal pain after fatty food intake and simple upper abdominal pain were 70% and 75%, respectively. Other single symptoms showed far lower relief rates after cholecystectomy.

In **chapter 4** the objective was to evaluate whether sonographic findings could predict relief of upper abdominal pain after cholecystectomy. A follow-up study of patients who underwent laparoscopic cholecystectomy for gallstone disease showed that the sonographic signs: gallbladder distension, wall thickness ≥ 3 mm and stone impaction in the cystic duct were associated with relief of biliary pain after cholecystectomy. In operated patients with one of these findings the predicted relief rate for upper abdominal pain increased from 75% to ±90%. Grit, defined as stones ≤ 3 mm, present on preoperative sonography was associated with persistence of upper abdominal pain. We concluded that sonography might be of value in the selection of patients who will benefit from laparoscopic cholecystectomy.

In **chapter 5** the value of a combination of patient characteristics and pre-operative symptoms, and the additional value of sonographic findings in the prediction of clinical outcome after cholecystectomy was evaluated. Of all included patients 89% presented with upper abdominal pain. Of these 68% fulfilled the definition of biliary pain: a severe, steady pain lasting more than one hour. In 96% of the patients upper abdominal pain was accompanied by one or more abdominal symptoms. Of the patients with biliary pain 32% still had complaints of (mild) upper abdominal pain after cholecystectomy. It was found that pre-operative flatulence, severe acid regurgitation, bloating and belching (eructation) were prognostic for the persistence of upper abdominal pain and dyspepsia with a probability of more than 40%. Sonographic findings did not add significantly to the predictive value of these symptoms. In patients with a low likelihood of upper abdominal pain relief (<60%) the presence of wall thickness ≥ 3 mm or stone impaction was associated with higher relief rates for upper abdominal pain (70% in patients with sonographic findings opposed to 33% in patients without these findings) but these associations did not reach statistical significance. Further studies with higher power should explore the association between sonographic findings and symptom relief in these specific subgroups. Particularly when the likelihood of post-operative symptom relief is almost fifty percent further prognostic information is needed.

The term 'biliary pain' suggests specificity for gallstone disease that we could not confirm. This term should therefore be used with caution. Too many patients will be operated because of the existence of this single symptom. In particular when biliary pain is accompanied by other abdominal symptoms, like acid regurgitation, bloating and belching, the outcome of cholecystectomy will be less favourable. The estimated likelihood of post-operative symptom relief should be based on the complex of patient characteristics and the symptoms with which the patient presents. To clarify the effect of cholecystectomy on abdominal symptoms in patients with gallstones a randomised-controlled trial is needed.

As therapy for gallstones has become safer and easier to perform it has become increasingly attractive to consider treating persons with gallstones. In making decisions about treatment clinicians and patients should consider that management strategies could aim at two distinct goals: relief of symptoms related to gallstones, and the prevention of biliary complications or death. **Chapter 6** presented a quantitative evaluation of the risks of surgical and 'watchful waiting' management strategies, and the difference between these strategies in long-term symptom-free status and life expectancy of the patient. To prevent biliary complications or death, immediate laparoscopic cholecystectomy was found to be the preferred strategy for both sexes at all ages, assuming that the gallstones were symptomatic. The choice of treatment depends on the risk of conversion to open cholecystectomy. A 70-year-old man with a conversion risk greater then 28% should choose expectant management in order to have the best life expectancy. To prevent biliary pain the gain in time spent without biliary pain by choosing laparoscopic cholecystectomy was considerably. This gain ranged from 10.7 years in women at age 30 to 2 years in men at age 70. Choice of treatment in terms of time spent symptom-free depended on the likelihood of symptom persistence after cholecystectomy. A likelihood

of more then 30 % for persistence of symptoms favoured the choice of expectant management in all patients.

We concluded that in patients with gallstones and abdominal symptoms other than single biliary pain, the option of expectant management should be considered in patients with low symptom relief rates after cholecystectomy and in older men with a high risk for conversion to open cholecystectomy. Most studies evaluating the post-operative outcome of cholecystectomy are uncontrolled. Firm estimates of post-operative outcome can only be reached by performing randomised trials. Further research in this area is needed.

Appendix

J Clin Gastroenerol 2000;30:101-2

To the Editor: In their informative analysis on the relation between abdominal symptoms and gallstones, Thijs *et al.*[1] note an important controversy in the literature. Review of earlier studies revealed conflicting results on the association between gallstones and food intolerance. The suggestion that the association between food intolerance and gallstones was possibly biased by inclusion of patients with a previous gallstone diagnosis and by confounding with pain patterns is not compatible with the results of one well-designed study[2]. The association in this study was so strong (odds ratio (OR), 14.0, 95% confidence interval (CI), 6.24-13.01) that it could not be explained by confounding alone. This finding was already noted by the authors in a previous meta-analysis (OR, 14.0, 95% CI, 9.13-21.66)[3].

It is not the erroneously reported 95% CI that we want to correct here, but rather the odds ratio itself. Reviewing the article by Peter *et al.*[2] we conclude that Thijs *et al.*[1] misinterpreted the data of this study. Peter *et al.*[2] presents the sensitivity and false-positive rate of food intolerance for the diagnosis of gallstones. Their figures are given in percentages (24% of 91 patients with 'asymptomatic' gallstones and 62% out of 165 patients with 'symptomatic' gallstones reported food intolerance versus 39% of 1122 patients without gallstones). Thijs *et al.*[1] calculated an OR based on these figures but interpreted the percentages as numbers of patients. Recalculation results in an OR of 1.5. Furthermore, based on their own results, Peter *et al.*[2] concluded - unlike Thijs *et al.*[1] - that there is only a weak relation between food intolerance and gallstones.

The conflicting results found in the literature may be less controversial than they seem, and may be well explained by the selection bias noted by Thijs *et al.*[1] Their conclusion therefore should be that there is no evidence for a relation between gallstones and food intolerance.

MY Berger
TC olde Hartman

Reply

To the editor: We are grateful to Berger and olde Hartman for having detected an error in our meta-analysis1 . As they point out, recalculation of the results of Peter *et al.*[2] for food intolerance and gallstone disease yields an odds ratio of 1.5; the 95% confidence interval is (1.11-1.95). The pooled odds ratio in our review can be recalculated as 1.6 (1.24-2.09), which is indeed very different from 9.0 (6.24-13.01) as initially reported. We proposed selection bias as an explanation for inconsistencies between clinical studies and screening studies[1,3]. Screening studies do not suffer from this bias. Janzon *et al.* found a pos-

itive association between gallstones and food intolerance (odds ratio 3.1(1.5-6.54))4, whereas three other screening studies showed no association (odds ratio 0.9 (0.52-1.54); 1.0 (0.11-9.43); one publication omitted exact data needed for the calculation of the odds ratio)[1,5,6]. Rather than concluding that there is no evidence for a relation between gallstones and food intolerance, as suggested by Berger and olde Hartman, we would conclude that the evidence remains inconsistent. Therefore, we maintain that the topic remains controversial and that it is worthwhile to pay attention to relief of food intolerance in trials of different treatment modalities for gallbladder disorders.

Carel Thijs

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Samenvatting

Het doel van dit proefschrift was om buikklachten te identificeren die het meest gerelateerd zijn aan galstenen. Een tweede doel was te evalueren of de aanwezigheid van deze bovenbuikklachten de symptomatische uitkomst na cholecystectomy kan voorspellen.

In eerste instantie is de associatie tussen buikklachten en de aanwezigheid van galblaasstenen geëvalueerd. **Hoofdstuk 1** presenteert de resultaten van een systematisch literatuur onderzoek van studies die de diagnostische waarde van buikklachten voor de aanwezigheid van galblaasstenen onderzochten. "Galsteenkoliek" gedefinieerd als een ernstige, continue bovenbuikpijn die meer dan 1 uur duurt, was het enige symptoom dat consistent en significant gerelateerd was aan de aanwezigheid van galstenen. Er werd een statistisch significant verschil gevonden tussen de diagnostische waarde van galsteenkolieken in studies waarin at random gekozen groepen mensen werden gescreend voor galstenen en de diagnostische waarde in studies die een naar de kliniek verwezen populatie onderzochten. Deze bevinding werd bevestigd door de bevindingen uit een studie van Thijs et al. In een screenings situatie vonden deze auteurs geen relatie tussen galsteenkolieken en de aanwezigheid van galstenen. In een studie van patiënten die waren verwezen voor een echografie van de galblaas was deze relatie echter wel aantoonbaar. Symptomen in een screenings populatie zullen milder zijn dan in een klinische setting, omdat de verwezen patiënten zich in een verder gevorderd stadium van de ziekte zullen bevinden. Van de andere kant kan het zijn dat symptomen in de gescreende populatie zo zeldzaam zijn, dat de aantallen te klein zijn om een statistisch significante associatie aan te tonen. De eerste verklaring voor onze bevinding werd bevestigd door het

feit dat de relatie tussen "galsteenkoliek" en galstenen sterker werd naarmate de ernst van de aandoening in de bestudeerde patiënten groter was. In ernstig zieke patiënten werd een OR van 4.1, 95% betrouwbaarheidsinterval 2.8 tot 6.1, gevonden. In de overige patiënten was het onderscheidend vermogen van "galsteenkolieken" tussen patiënten met en zonder galstenen, niet klinisch relevant.

Een associatie tussen voedsel- en vetintolerantie en de aanwezigheid van galstenen werd uitgesloten. Deze conclusie was niet in overeenstemming met de bevindingen van Thijs *et al.* Deze auteurs concludeerden dat de relatie tussen voedselintolerantie en galstenen controversieel blijft. Deze auteurs baseerden hun conclusie op een hoge gepoolde odds ratio (14.0, 95% BI 9.13 tot 21.7) die zij berekenden in een eerdere metanalyse over dit onderwerp. Deze hoge OR bleek echter gebaseerd op een verkeerde interpretatie van de gegevens uit een enkele studie.

In de dagelijkse praktijk zal de clinicus zich niet baseren op afzonderlijke symptomen maar op een patroon van symptomen waarmee de patiënt zich presenteert. Ons volgende doel was om een combinatie vanbuikklachten aan te tonen die het meest geassocieerd was met de aanwezigheid van galblaasstenen. In **hoofdstuk 2** worden de resultaten van een studie gepresenteerd waarin patiënten verdacht van galsteenlijden worden vervolgd. De associatie tussen "galsteenkoliek" en galstenen wordt in deze studie bevestigd. "Galsteenkoliek", braken en geelzucht bleken in een multivariaat model voorspellend te zijn voor de aanwezigheid van galstenen. Deze symptomen konden echter niet worden gebruikt om een klinisch relevant onderscheid te maken tussen patiënten mét en zonder galstenen. Wij formuleerden de hypothese dat braken alleen aan galsteenlijden gerelateerd is in ernstig zieke patiënten en dat het moet worden beschouwd als een begeleidend verschijnsel, meer dan dat het daadwerkelijk door de aanwezigheid van galblaasstenen wordt veroorzaakt.

Gebaseerd op deze twee onderzoeken concluderen wij dat de aanwezigheid van galstenen niet kan worden voorspeld door de aanwezigheid van bepaalde buikklachten of een combinatie van deze klachten.

In **hoofdstuk 3** was het doel om buikklachten van patiënten met galstenen aan te wijzen die zouden verdwijnen na cholecystectomie. Dit hoofdstuk bevat de resultaten van een systematisch literatuuronderzoek van studies die het verdwijnen van buikklachten na cholecystectomie onderzoeken. Daarnaast worden de resultaten gepresenteerd van een studie waarin patiënten verdacht van galstenen worden vervolgd. Vrijwel alle patiënten met "galsteenkoliek" (90-95%) hadden hier, na cholecystectomie, geen last meer van. Dit hoge percentage patiënten met verlichting van hun klacht was niet specifiek voor de geopereerde patiënten, ook niet-geopereerde patiënten zonder galstenen, maar met "galsteenkolieken", bleken na een periode van gemiddeld 14 maanden van hun klacht af te zijn (80%). Verlichting van bovenbuikpijn na vet eten en van eenvoudige bovenbuikpijn werd gevonden in respectievelijk 70% en 75% van de patiënten. Andere afzonderlijke symptomen tonen veel lagere percentages postoperatieve verlichting.
In **hoofdstuk 4** werd beoordeeld of echografische bevindingen het verdwijnen van bovenbuikklachten na een cholecystectomie konden voorspellen. In een vervolgstudie van

patiënten die een laparoscopische cholecystectomie hadden ondergaan kon worden aangetoond dat een verdikte galblaaswand ≥ 3 mm en impactie van een galsteen in een galgang waren geassocieerd met verlichting van klachten na cholecystectomie. In geopereerde patiënten met een van deze echografische bevindingen steeg de kans op postoperatieve verlichting van bovenbuikpijn van 75% naar bijna 90%. Gruis gedefinieerd als stenen ≤3 mm, aangetoond op een preoperatieve echo, was geassocieerd met het persisteren van bovenbuikpijn. Wij concluderen dat bevindingen op echografie mogelijk van waarde kunnen zijn bij de selectie van patiënten met galstenen en buikklachten, die baat zullen hebben bij een laparoscopische cholecystectomie.

In **hoofdstuk 5** wordt de voorspellende waarde van een combinatie van bovenbuikklachten en patient karakteristieken op de symptomatische uitkomst van cholecystectomie bestudeerd. Daarbij wordt bekeken of echografische bevindingen een toegevoegde waarde hebben aan de voorspellende waarde van buikklachten alleen. Van alle geïncludeerde patiënten presenteerde 89% zich met bovenbuikpijn. Van deze patiënten voldeed 68% aan de definitie van "galsteenkoliek": een ernstige, continue bovenbuikpijn die langer dan een uur duurt. In 96% van de patiënten werd de bovenbuikpijn vergezeld van een of meerdere andere bovenbuikklachten. Van de patiënten met "galsteenkoliek" had 32% postoperatief nog klachten van (milde) bovenbuikpijn. Preoperatieve klachten van flatulentie, ernstig maagzuurbranden, een opgeblazen gevoel en boeren bleken prognostisch voor het persisteren van bovenbuikpijn en dyspepsie met een kans van meer dan 40%. Echografische bevindingen konden geen statistisch significante verbetering van deze voorspelling te weeg brengen. In patiënten met een lage kans op verlichting van hun bovenbuikpijn (<60%) was de aanwezigheid van een verdikte galblaaswand ≤3 mm op de echo of een geïmpacteerde steen, geassocieerd met een grotere kans op het verdwijnen van de bovenbuikspijn (70 % in patiënten met deze bevindingen op de echo en 33% in patiënten zonder deze bevindingen). Maar deze associatie was niet statistisch significant. Toekomstig onderzoek met grotere aantallen patiënten, zal zich moeten richten op deze specifieke subgroepen om de associatie tussen echografische bevindingen en het verdwijnen van bovenbuikklachten verder te evalueren.

De term "galsteenkoliek" suggereert een specifieke relatie met galsteenlijden die wij niet hebben kunnen bevestigen. Deze term moet daarom voorzichtig worden gebruikt. Teveel patiënten zijn geopereerd vanwege de aanwezigheid van dit symptoom. In het bijzonder wanneer een galsteenkoliek wordt vergezeld van andere symptomen zoals brandend maagzuur, een opgeblazen gevoel, boeren en flatulentie, zal de uitkomst van cholecystectomie slecht zijn. De kans op postoperatieve verlichting van de klachten moet gebaseerd zijn op een patroon van klachten waarmee de patiënt zich presenteert. Om tot een juiste schatting van postoperatieve symptoomverlichting te komen zal men een gerandomiseerde trial moeten verrichten.

Sinds de behandeling van galstenen veiliger en eenvoudiger is geworden wordt het steeds antrekkelijker om patiënten met galstenen voor behandeling in aanmerking te laten komen. In de besluitvorming over behandeling zullen patiënt en arts zich moeten realiseren dat behandeling zich op twee doelen kan richten: verlichting van de klachten

die worden toegeschreven aan galstenen en het voorkomen van complicaties en overlijden ten gevolge van deze complicaties.

Hoofdstuk 6 presenteert de resultaten van een beslisanalyse waarin de risico's van direct opereren worden afgewogen tegen de risico's van een afwachtende strategie. Gekeken wordt naar de verschillen tussen deze strategieën in levensverwachting en tijd levenslang doorgebracht zonder klachten. Om complicaties van galsteenlijden of overlijden hieraan te voorkomen is directe laparoscopische cholecystectomie de beste optie voor alle patiënten, ongeacht hun leeftijd en geslacht, mits de klachten ook daadwerkelijk veroorzaakt worden door de galstenen. De keuze van behandeling, afwachten of direct opereren, is afhankelijk van het risico van conversie van laparoscopische naar open cholecystectomie en leeftijd van de patiënt. Een 70-jarige man met een conversierisico groter dan 28% zou moeten kiezen voor een afwachtende houding om een betere levensverwachting te hebben.

Door te kiezen voor directe laparoscopische cholecystectomie werden enkele jaren zonder galsteenkolieken gewonnen. Een vrouw van 30 jaar won zo 10.7 jaren zonder galsteenkolieken en een man van 70 won 2 jaar zonder galsteenkoliek. In termen van gespendeerde tijd zonder galsteenkolieken hing de keuze voor een behandeling af van de kans op het persisteren van de klachten na cholecystectomie. Met een kans van meer dan 30% op het postoperatief persisteren van klachten is een patiënt beter af door een afwachtend beleid te kiezen.

We concluderen dat in patiënten met galstenen en buikklachten anders dan enkel en alleen 'galsteenkolieken', de optie van een afwachtend beleid moet worden overwogen wanneer een kleine kans (<70%) op postoperatieve klachtenverlichting bestaat. Tevens verdient een afwachtend beleid de voorkeur bij 70-jarige mannen met een hoog risico op conversie van laparoscopische naar open cholecystectomie.

De waarde van echografische bevindingen om de kans op postoperatieve klachtenverlichting te voorspellen moet worden onderzocht in subgroepen van patiënten waarbij deze kans klein is (<70%). De meeste studies die de symptomatische uitkomst na cholecystectomie hebben onderzocht zijn ongecontroleerd. Harde uitspraken over postoperatieve uitkomsten kunnen alleen gedaan worden op basis van een gerandomiseerde trial. Toekomstig onderzoek moet zich hier dan ook op richten.

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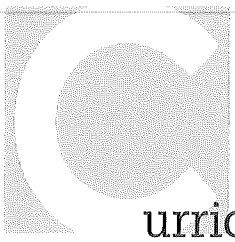

urriculum vitae

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1968 - 1975	Atheneum B, Scholengemeenschap 'St. Thomascollege' te Venlo
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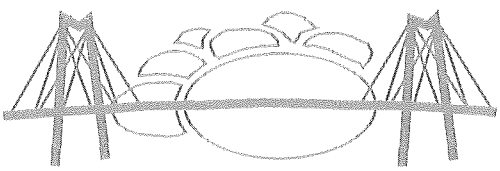
APPENDIX

Sonographic signs of gallbladder stone disease



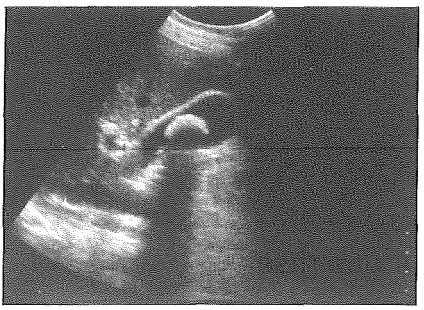
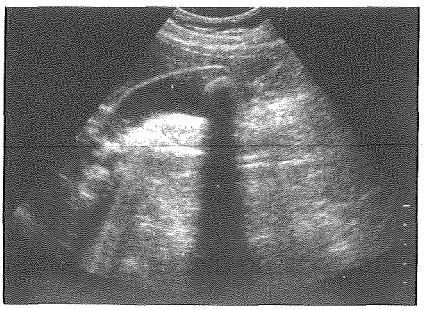



Figure 1a/b

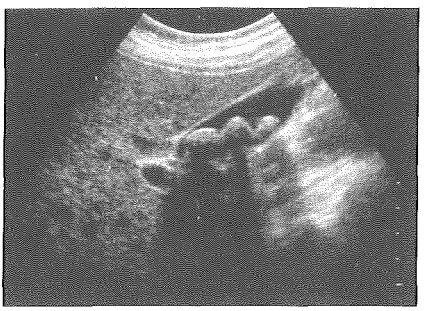


Figure 2

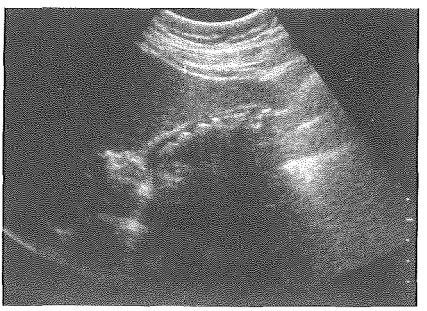


Figure 3

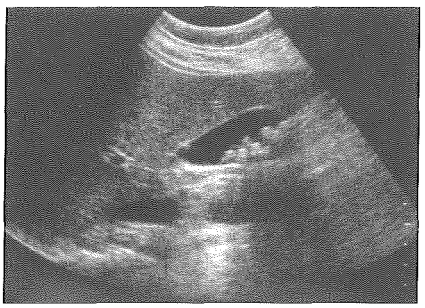
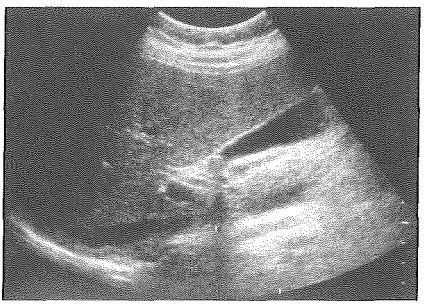



Figure 4a/b

Figure 1a: single stone.
Figure 1b: The stone falls in the gallbladder fundus in an upright position.
Figure 2: multiple stones.
Figure 3: contracted gallbladder, the gallbladder lumen contains only stones without normal surroundig bile.
Figure 4a: stone impaction in the cystic duct or the gallbladder neck.
Figure 4b: Impaction was considered present when stones did not move with the change in patient position, especially in an upright position.

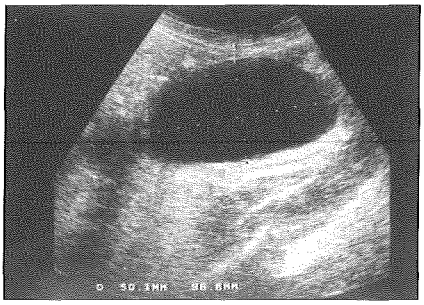


Figure 5

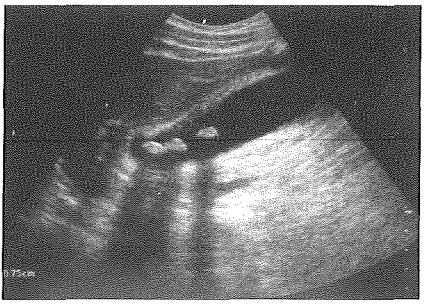
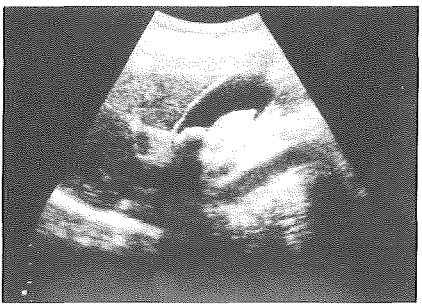


Figure 6



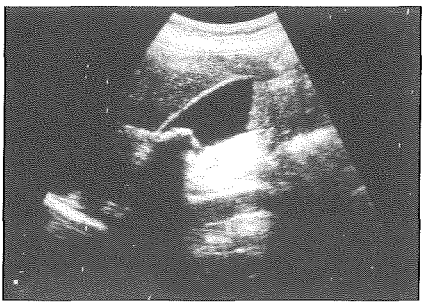


Figure 7a/b

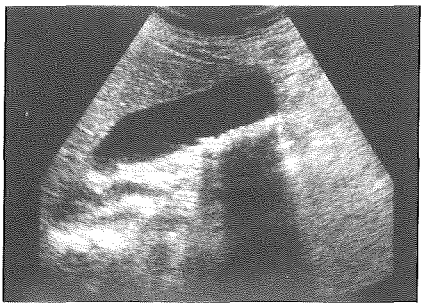


Figure 8

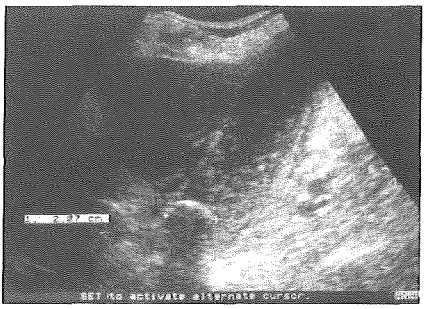


Figure 9

Figure 5: distended gallbladder or hydrops, diameter perpendicular to the longitudinal axis of ≥4.5 cm.
Figure 6: thickened gallbladder wall of ≥3 mm.
Figure 7a: Gallstone in gallbladder neck and sludge.
Figure 7b: In an upright position the gallstone is impacted in the gallbladder neck and the sludge is lying on the bottom of the gallbladder.
Figure 8: grit, stones ≤3 mm.
Figure 9: acute cholecystitis, thickened gallbladder wall, fluid in wall and also around the gallbladder and an impacted stone.

KLACHTENPROFIELLIJST

S.V.P. bij ieder symptoom **1 vakje** aankruisen.

Heeft u **de afgelopen MAAND**, een of meerdere malen last gehad van:

	geen last	weinig last	vrij veel last	heel veel last
1. Misselijkheid	☐	☐	☐	☐
2. Braken	☐	☐	☐	☐
3. Opgeblazen gevoel	☐	☐	☐	☐

	geen last	weinig last	vrij veel last	heel veel last
4. Boeren/oprispingen	☐	☐	☐	☐
5. Brandend maagzuur	☐	☐	☐	☐
6. Krampende bovenbuikspijn rechts	☐	☐	☐	☐
7. Krampende bovenbuikspijn rechts, alleen na vet eten	☐	☐	☐	☐

	geen last	weinig last	vrij veel last	heel veel last
8. Bovenbuikspijn > 1 uur rechts	☐	☐	☐	☐
9. Obstipatie (verstopping)	☐	☐	☐	☐
10. Diarrhee (snelle stoelgang)	☐	☐	☐	☐

	geen last	weinig last	vrij veel last	heel veel last
11. Winderigheid	☐	☐	☐	☐
12. Koorts	☐	☐	☐	☐
13. Geelzucht	☐	☐	☐	☐