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Is cholecystectomy effective treatment for symptomatic gallstones? Clinical outcome after long-term follow-up

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The expectation that cholecystectomy is effective treatment for symptomatic gallstones is not always achieved in surgical practice. The impact of cholecystectomy on the relief of gastrointestinal symptoms was evaluated in 92 patients followed up after surgery for a mean of 31.1 months (range 12–83 months). Abdominal pain continued to be present, or arose *de novo*, in 28 (30.4%) patients. Pain-free outcome after cholecystectomy was associated with a preoperative clinical diagnosis of biliary colic, fatty food intolerance, and a thick-walled gallbladder on ultrasound ($P=0.02$). Logistic regression associated a thick-walled gallbladder, elevated γ-glutamyl transpetidase, body mass index <26, fat intolerance, and normal bowel habit with good postoperative results ($P=0.001$). Application of each of these five factors to a clinical index failed to predict long-term pain-free outcome after cholecystectomy. Abdominal bloating ($P=0.03$), dyspepsia ($P<0.001$), heartburn ($P<0.007$), fat intolerance ($P<0.001$), nausea ($P=0.001$) and vomiting ($P<0.001$) were significantly improved after cholecystectomy, but diarrhoea, constipation and excessive flatus were not. Outcome benefit ratios confirmed that vomiting (0.96), nausea (0.87), dyspepsia (0.67), fat intolerance (0.57) and heartburn (0.51) were relieved by surgery. Cholecystectomy improved symptoms compared with a matched control group, suggesting that surgery remains the gold standard treatment of symptomatic gallstones.

The acceptance of laparoscopic cholecystectomy by general surgeons has broadened the indications thought to justify the procedure and has increased the number of cholecystectomies performed *(1–3)*. However, a significant proportion of patients continue to experience symptoms related to the gastrointestinal tract after cholecystectomy *(4–7)*, and previous studies have shown that symptomatic outcome is similar whether the gallbladder is removed by the laparoscopic or open method *(8–10)*. Symptoms after surgery may be pre-existing or arise *de novo*. The aims of this study were to identify which symptoms were improved after cholecystectomy, to ascertain if the prevalence of symptoms after cholecystectomy was different to the prevalence of similar symptoms in a control group of patients, and to determine if a method could be evolved for selecting patients who would benefit by symptomatic relief after laparoscopic cholecystectomy.

Methods

A consecutive series of 102 patients who underwent cholecystectomy in one surgical unit between 1989 and 1995 were recalled postoperatively for structured interview and physical examination. In all, 92 patients responded and formed the study population, with a

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mean follow-up of 31.1 months (range 12–83 months). Six patients who had moved out of the area could not be contacted, and there were four deaths unrelated to gallbladder disease. The preoperative symptoms assessed in relation to clinical outcome in this study included abdominal bloating, nausea, vomiting, heartburn, indigestion, diarrhoea, constipation and flatus. Biliary colic was defined in this study as right upper quadrant or epigastric pain that might radiate inferior to the shoulder blade or to the shoulder tip, that waned over a period of several hours. Acute cholecystitis was distinguished from biliary colic by the severity of abdominal tenderness, fever and an elevated white blood cell count. 'Atypical' biliary colic was not considered to be of gallbladder origin. Other factors studied were age, gender, body mass index, smoking, alcohol consumption, ultrasonographic findings and serum liver biochemistry.

Data were analysed using non-parameteric analysis in the following manner:

1 Postcholecystectomy abdominal pain, after a minimum follow-up period of 12 months, was categorised as an absolute endpoint. Patients were investigated to exclude retained or recurrent stones using serum liver biochemistry and ultrasound, proceeding only to endoscopic retrograde cholangiopancreatogram (ERCP) and oesophagogastroduodenoscopy (OGD) where clinically indicated. Preoperative symptoms were compared with the presence or absence of postoperative pain using the χ^2 test with Yates' correction. Variables significant at $P<0.05$ were considered to be individually but not independently predictive of symptomatic outcome with reference to postoperative pain.
2 Variables were analysed using logistic regression, including a stepwise forward approach, to assess the relationship to postcholecystectomy abdominal pain. Any variables appearing significant in this analysis were then used to create a potential model by which patients could be selected for cholecystectomy, by application of the predictive model to this retrospective series.
3 Symptoms before and after surgery were compared using McNemar's test to evaluate whether cholecystectomy had been of benefit. Outcome benefit ratios for each symptom after cholecystectomy were also derived, using the formula: the difference between the number of patients with each symptom preoperatively and those who developed it postoperatively (persistent and *de novo*), divided by the number of patients exhibiting the symptom preoperatively *(8)*. An outcome benefit ratio closer to one therefore indicated favourable treatment of a given symptom by surgery.
4 The prevalences of gastrointestinal symptoms in the precholecystectomy and postcholecystectomy group were compared with a defined control population. The control group consisted of 90 patients who attended surgical outpatients with breast conditions ($n=30$), groin hernias ($n=30$) and varicose veins ($n=30$). A given symptom was considered to be positive in both the test and control groups if present on more than one occasion per month over the preceding year. If the prevalence of symptoms in the precholecystectomy group was higher than in the control population while the prevalence of symptoms in the postcholecystectomy group was not, then cholecystectomy could have been considered 'curative'. Groups were compared using the χ^2 test with Yates' correction.

Results

The patient sample and study variables are listed in Table I. All 92 patients experienced abdominal pain before surgery. The diagnosis of biliary colic when taken in context with the clinical presentation was made in 52 patients. Fifty-seven gallbladders were removed by the laparoscopic method while 35 were excised conventionally at open surgery. All patients had the presence of gallstones confirmed on ultrasound examination and at surgery. A total of 28 (30.4%) patients continued to have abdominal pain after cholecystectomy; 13 patients had a similar pain to the preoperative condition and 15 patients a distinct pain. This was graded separately from wound pain which affected 16 (17.4%) patients. Despite this, 86 (93.5%) patients were satisfied with the outcome of their operation. Histology confirmed features of chronic cholecystitis in 91 (98.9%) of the patients studied and acute cholecystitis was reported in one (1.1%) patient. Of the 13 patients who had a persistent similar pain after surgery, 12 continued to have pain at the time of recall for interview, compared with seven of the 15 patients who

Table I. Details of patients who had cholecystectomy for symptomatic gallstones

Sample size:	$n=92$ patients (female $n=70$; male $n=22$)
Mean age (range):	51.2 (24–84) years
Mean body mass index (range):	25.7 (17.6–47.4)
Mean follow-up time (range):	31.1 (12–83) months
Indications for surgery (%):	
Biliary colic	$n=39$ (42.4)
Previous acute cholecystitis*	$n=22$ (23.9)
Previous acute pancreatitis	$n=13$ (14.1)
Previous obstructive jaundice	$n=7$ (7.6)
Previous ascending cholangitis	$n=1$ (1.1)
Non-specific pain	$n=10$ (10.9)
Abdominal pain before surgery:	$n=92$
Right upper quadrant (%):	$n=45$ (48.9)
Epigastric (%):	$n=41$ (44.6)
Other site (%):	$n=6$ (6.5)
Abdominal pain after surgery:	
Same pain	$n=13$
Different pain	$n=15$
Wound pain	$n=16$

*13 patients with an episode of acute cholecystitis also gave a history of biliary colic

Table II. Individual variables that predict pain-free outcome after cholecystectomy

Variables	*Postoperative outcome*		χ^2	*P-value*
	Pain-free (n=64)	*Pain present (n=28)*		
Abdominal bloating	28	12	0.02	0.88
Nausea	49	20	0.07	0.79
Vomiting	31	15	0.05	0.82
Heartburn	30	11	0.20	0.66
Indigestion pain	41	17	0.01	1.94
Right upper quadrant pain	30	15	0.49	1.49
Biliary colic	42	10	5.93	0.02*
Fatty food intolerance	34	23	5.78	0.02*
Diarrhoea	8	5	0.13	0.72
Constipation	15	6	0.01	0.95
Excessive flatus	16	6	0.01	0.92
Jaundice	10	2	0.60	0.44
Gender Male	19	3		
Female	45	25	2.88	0.09
Thick gallbladder wall	41	10	5.24	0.02*
Liver biochemistry				
↑ Bilirubin (0–17 μmol/l)	16	2	2.89	0.09
↑ ALP (30–100 iu/l)	22	6	0.99	0.32
↑ ALT (5–40 μmol/l)	19	6	0.32	0.57
↑ GGT (0–60 iu/l)	26	7	1.44	0.23

ALP = alkaline phosphatase; ALT = alanine transferase; GGT = γ-glutamyl transpeptidase
*Statistically significant at $P < 0.05$

had a different pain after cholecystectomy. In all, 32 patients returned to work (or normal activity if retired) in <2 weeks, 32 patients between 2 and 4 weeks and 28 patients after 4 weeks. There was no relationship between return to work time and the presence or absence of chronic postopertaive pain or symptoms.

When considered individually, only a clinical diagnosis of biliary colic, preoperative fatty food intolerance and the presence of a thick-walled gallbladder on ultrasonography were significantly associated with pain-free outcome after surgery (Table II). The site of pain alone, categorised as right upper quadrant, epigastric or back pain, was unhelpful in predicting surgical outcome. Postcholecystectomy abdominal pain after long-term follow-up was not related to age, smoking, alcohol consumption, grade of surgeon, open or laparoscopic cholecystectomy, nor previous episodes of acute cholecystitis, acute pancreatitis, obstructive jaundice or ascending cholangitis.

Preoperative symptoms considered together, using a logistic regression model with postcholecystectomy abdominal pain as an endpoint, were of limited value in the prediction of good long-term clinical outcome. When all the variables studied were analysed using a stepwise forward approach, only five factors were found to be significant. These were a thick-walled gallbladder on ultrasound examination, an elevated γ-glutamyl transpeptidase (>60 iu/l), a low body mass index (<26.0, the median value of this study group), fatty food intolerance, and the presence of normal bowel habit. Logistic regression using these significant variables alone produced a model that significantly predicted a pain-free outcome after cholecystectomy, with a χ^2-value of 18.2 and an overall *P*-value of logit estimates of 0.001 (Table III). Each of these factors was then applied unweighted, retrospectively, to this series. When any one factor was present, the sensitivity in predicting a postoperative pain-free course was 8%, with a specificity of 82%. When two factors were present, the sensitivity increased to 30% and the specificity was 79%, with similar figures for three and four positive factors of sensitivity = 36%, specificity = 71%, and sensitivity = 23%, specificity = 75%, respectively. However, when all five factors were present, the sensitivity decreased to 3%, while the specificity increased to 96%. Although this model theoretically predicted a score that could have statistical significance when applied to an index to predict pain-free

Table III. Potential model selected from logistic regression analysis to predict good outcome after cholecystectomy

Variable	*Coefficient*	*P-value*
Thick-walled gallbladder	1.26	0.02
Elevated GGT (>60 iu/l)	0.72	0.03
Body mass index (<26.0)	0.86	0.08
Fatty food intolerance	0.95	0.13
Normal bowel habit	1.5	0.44
Number of observations = 92		
χ^2 test of overall model = 18.2		
Overall *P*-value of logit estimates = 0.001		

GGT = γ-glutamyl transpeptidase

Table IV. Assessment of the effect of cholecystectomy on individual symptoms before and after surgery in 92 patients

	Postoperative symptom				
	Present persistent	*De novo*	*Absent cured*	*Never suffered*	*McNemar's test P-value*
Gas bloat	18	9	22	43	0.03
Nausea	9	0	60	23	<0.001
Vomiting	2	0	44	46	<0.001
Heartburn	13	7	28	44	0.007
Dyspepsia	15	4	43	30	<0.001
Fat intolerance	26	3	41	22	<0.001
Diarrhoea	7	5	6	74	1.0
Constipation	12	2	9	69	0.07
Flatus	11	15	11	55	0.556

outcome after cholecystectomy, the score did not reach clinical significance in our series.

When preoperative symptoms were compared against themselves before and after cholecystectomy using McNemar's test, abdominal bloating, indigestion pain, heartburn, fatty food intolerance, nausea and vomiting were significantly improved after surgery, but diarrhoea, constipation and excessive flatus were not (Table IV). Postoperative symptoms relating to the gastrointestinal tract may persist from the preoperative clinical presentation, or arise *de novo* after cholecystectomy. Each of the symptoms studied were capable of arising *de novo* except nausea and vomiting, suggesting the complex aetiology attributable to the postcholecystectomy syndrome.

The outcome benefit ratios of each symptom after cholecystectomy are shown in Fig. 1. Vomiting, nausea, dyspepsia, fat intolerance and heartburn had high outcome benefit ratios. These were symptoms most likely to be improved by surgery and therefore most likely to be of gallbladder origin. Symptomatic outcome assessed after cholecystectomy using McNemar's test (Table IV) had outcome benefit ratios (Fig. 1) were closely associated, identifying the same factors that were likely to benefit from surgery. The prevalence of symptoms after cholecystectomy was no different between patients who had their gallbladders excised laparoscopically or at open operation.

The control group consisted of 90 patients presenting to surgical outpatients with a breast condition ($n=30$), hernias ($n=30$) and varicose veins ($n=30$). The control sample, consisting of 65 women (72.2%) and 25 men with a mean age of 50.8 years (range 21–86 years) and mean body mass index of 25.1 (range 16.4–51.6), was well matched to the test population. The prevalence of upper gastrointestinal symptoms in the control group was found to be: abdominal bloating $n=20$ (22.2%), nausea $n=10$ (11.1%), vomiting $n=5$ (5.6%), heartburn $n=9$ (10%), dyspepsia $n=14$ (15.6%), upper abdominal pain $n=17$ (18.9%), and excessive flatus $n=23$ (25.6%). No difference was found between the prevalence of these symptoms in each of the breast, hernia or varicose vein control groups (χ^2 test with Yates' correction). The prevalence of symptoms in the control group was compared with the patients in the study population before and after cholecystectomy (Fig. 2). The following symptoms were significantly less prevalent in the control group compared with patients in the study before cholecystectomy: abdominal bloating ($\chi^2=8.36$, $P=0.003$); nausea ($\chi^2=73.02$, $P<0.001$); vomiting ($\chi^2=42.38$, $P<0.001$); heartburn ($\chi^2=25.57$, $P<0.001$); dyspepsia ($\chi^2=40.95$, $P<0.001$) and upper abdominal pain ($\chi^2=21.25$, $P<0.001$). There was no difference in the proportion of patients who considered excessive flatus a prominent symptom in the control group compared with the precholecystectomy group ($\chi^2=0.007$, $P=0.93$). After cholecystectomy, no significant difference was identified between the control and study group with regard to abdominal bloating ($\chi^2=0.86$, $P=0.35$); nausea

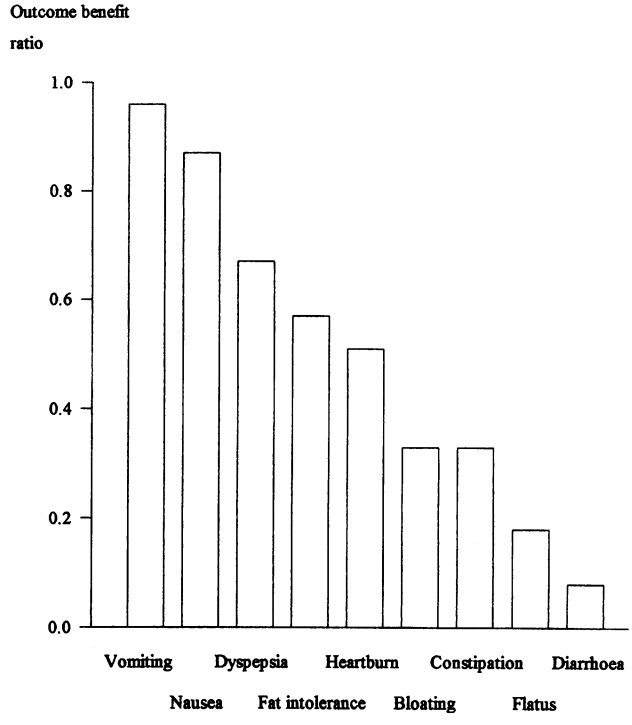

Figure 1. Outcome benefit ratios of individual symptoms compared before and after cholecystectomy. A ratio closer to 1.0 indicates greater symptomatic benefit from surgery, and thus increased likelihood of that symptom being of gallstone origin.

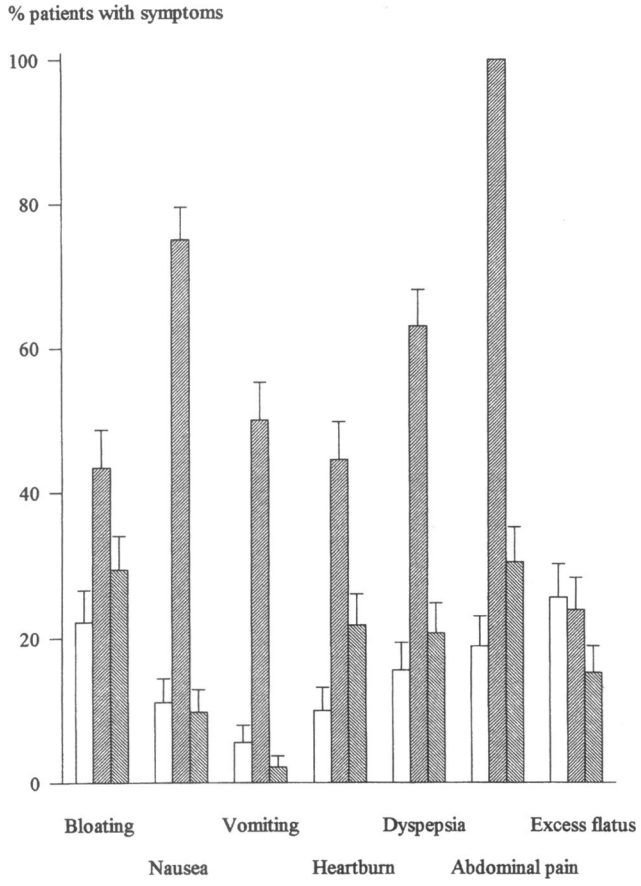

Figure 2. Prevalence (± standard error) of gastrointestinal symptoms in the control population (□, $n=90$) compared with the study population ($n=92$) before (▨) and after (▧) cholecystectomy.

($\chi^2=0.003$, $P=0.96$); vomiting ($\chi^2=0.64$, $P=0.42$); dyspepsia ($\chi^2=0.49$, $P=0.48$); upper abdominal pain ($\chi^2=2.67$, $P=0.102$), and excessive flatus ($\chi^2=2.40$, $P=0.12$). Although there was symptomatic improvement of heartburn after cholecystectomy (Table IV), with a significant outcome benefit ratio (Fig. 1), the prevalence of heartburn in the control group ($n=9$, 10.0%) remained lower than that of patients who had cholecystectomy ($n=20$, 21.7%), ($\chi^2=3.85$, $P=0.05$) (Fig. 2). These results suggest that all the symptoms studied apart from heartburn are improved by cholecystectomy to a prevalence comparable to that in the control group. Cholecystectomy therefore is curative for the majority of patients with symptomatic gallstones.

Discussion

As cholelithiasis can present with a complex combination of clinical symptoms *(4,11–13)*, gallstones found incidentally in the investigation of gastrointestinal symptoms may become falsely incriminated to explain pathology that arises outside the biliary tree *(14)*. Inappropriate cholecystectomies thus performed are likely to be associated with poor symptomatic outcome. This important clinical problem was addressed in our study. The prevalence of abdominal pain after cholecystectomy varies from 29% to 50% *(4,6,8,10)*, while symptom relief achieved by gallbladder excision varies from 42% to 88% *(5,7,15–17)*. A direct comparison between studies is precluded by variation in the definition of symptoms, the duration of follow-up and the stratification of postcholecystectomy symptoms into persistent and *de novo*. Table V summarises the results of recently published data on the symptomatic outcome after cholecystectomy *(4,8,10,13,16–18)*. In our study, a clinical diagnosis of biliary colic was associated with a pain-free outcome after surgery, but this relationship was neither exclusive nor a reliable predictor of good results. The aetiology of persistent or *de novo* symptoms after cholecystectomy is multifactorial *(12,13,19–23)*, and the relative risk of developing postcholecystectomy syndrome should be made clear to patients before surgery.

Using outcome benefit ratios, Vander Velpen *et al. (8)* identified that nausea, vomiting and heartburn were symptoms related to gallstones, a finding supported in our study. The resolution of heartburn after cholecystectomy was significant, as this suggests that the symptoms usually attributed to gastro-oesophageal reflux can be a manifestation of gallstone disease. Cholecystectomy may also predispose to compromised gastro-oesophageal sphincter competence leading to reflux *(20)*. In this study, we found that fatty food intolerance and dyspepsia were significantly improved after cholecystectomy, while Scriven *et al. (18)*, also reported high cure rates for upper abdominal colic, and for back and shoulder pain. We and others *(8,10,18,24)* have shown that patient expectation of cholecystectomy is not high, with 77% to 93.5% of patients pleased with the end result despite the persistence, or the development *de novo*, of symptoms. Patient assessment in isolation therefore does not represent an accurate relationship to the true outcome of individual symptoms. This observation challenges the results of those studies that do not consider the progress of each symptom after cholecystectomy, and also calls into question the reporting of postoperative outcome by patients alone.

The role of cholecystectomy in patients who have previously developed a complication of gallstone disease (such as acute cholecystitis, obstructive jaundice, gallstone-induced acute pancreatitis or ascending cholangitis) is well established but surgery for the treatment of symptoms alone can be controversial. Expert panels asked to consider the appropriateness of 252 patients who had previously undergone cholecystectomy in the North West Thames Regional Health Authority held widely varying opinions on excision of the gallbladder in individual cases *(25)*. In that study, an expert panel consisting of three gastroenterologists, two general physicians, two surgeons, one radiologist and one general practitioner agreed on the appropriateness of cholecystectomy in 41% of cases, considered that 30% of cases were operated on inappropriately, but could not reach a consensus in 29%. A second expert panel that consisted of nine surgeons, however, agreed on the appropriateness of surgery in 52%, considered 2% inappropriately operated

Table V. Summary of results from previous publications on symptomatic outcome after cholecystectomy

Author	Patients included (n)	Eligible patients excluded or missing* (n)	Outcome after surgery: Pain-free (n and/or %)	Symptom free (n and/or %): Dyspepsia	Heartburn	Nausea	Vomiting	Bloating	Flatus	Combined	Follow-up
Bates *et al. (6)*	278	0	73%	58%	N/A	81%	90%	60%	58%	N/A	2 years
Fenster *et al. (7)*	188	24	82%	N/A	N/A	N/A	N/A	N/A	N/A	44%	3 months
Gilliland and Traverso *(16)*	525	125	N/A	N/A	N/A	N/A	N/A	N/A	N/A	461	Mean 45 months (88%) (range 15–79 months)
Gunn and Keddie *(4)*	107	0	77%	69%	31%	N/A	N/A	N/A	N/A	N/A	2 years
Kingston and Windsor *(13)*	100	0	N/A	27/33 (80%)	N/A	N/A	N/A	N/A	N/A	N/A	Mean 13 months (range 3–36 months)
Konsten *et al. (17)*	325	26	N/A	N/A	N/A	N/A	N/A	N/A	N/A	265 (81.5)	Median 10 years (range 0.3–12 years)
McMahon *et al. (10)*	233	37	117/233 (50%)	201/233 (86%)	171/233 (73%)	199/233 (85%)	220/233 (94%)	162/233 (70%)	N/A	N/A	1 year
Ros and Zambon *(5)*	93	27	92/93 (99%)	24/46 (52%)	N/A	N/A	N/A	N/A	N/A	49/93 (53%)	2 years
Scriven *et al. (18)*	77	0	73%	55%	N/A	64%	N/A	49%	57%	N/A	1 year
Vander Velpen *et al. (8)*	124	36	43/53 (81%)	N/A	32/49 (65%)	25/34 (74%)	40/46 (87%)	N/A	8/32 (25%)	N/A	Median 9 months (range 6–30 months)

N/A = not analysed or could not be derived from the published data * Not including deaths from gallstone unrelated causes

upon, but could not agree on the indication for surgery in 44% of patients *(25)*. A preceding report by the same authors *(26)* using similar expert panel groups analysed the consensus opinion on a series of possible indications for cholecystectomy. Although a consensus was reached on 61% of indications by the surgical panel and 67% by the mixed panel, the surgical panel considered more indications appropriate for cholecystectomy compared with the mixed group (29% *vs* 13%) and fewer indications inappropriate than the mixed panel (27% *vs* 50%) *(26)*. Careful evaluation of symptoms may potentially identify patients who are most likely to benefit from cholecystectomy. This concept should be investigated further in a prospective clinical trial in which patients with symptoms that are predominantly associated with poor outcome from surgery are randomised into cholecystectomy *versus* no surgery groups.

A clinical score to predict good symptomatic relief after cholecystectomy, incorporating variables that are readily available to the clinician preoperatively, is of potential value in case selection for cholecystectomy. In this study, a clinical index based on a thick-walled gallbladder, elevated γ-glutamyl transpeptidase, body mass index, fat intolerance and normal bowel habit did not achieve clinical significance when applied to the test sample. The retrospective design of this study and the inclusion of unweighted variables to the score are important reasons that may account, in part, for this discrepancy. A further limitation of this and other studies is that not all patients who had postcholecystectomy symptoms had ERCP. In a study of patients with significant symptoms after cholecystectomy *(27)*, 8% of postcholecystectomy patients without jaundice had retained stones detected by ERCP and 25% had an abnormal pancreatogram. ERCP is therefore the investigation of choice for persistent and severe symptoms, and should be offered to all patients in future studies to assess persistent postcholecystectomy symptoms. Although our data were compared with a matched control group attending outpatients for causes outside the gastrointestinal tract, this study did not take into consideration the wide variation in the natural history of gallstone disease nor the placebo effect of surgery. Potential symptomatic and asymptomatic gallstones in our control group were not known as these patients did not have ultrasound assessments of their gallbladders. The aim of our control group, however, was to compare the prevalence of gastrointestinal symptoms after cholecystectomy with that in the local population. The prevalence of dyspepsia in community studies in England and Scotland ranges from 33% to 40%, of whom only 17% to 29% of symptomatic patients seek medical advice *(28)*. The observed prevalence of dyspepsia in our control group was therefore likely to underestimate the actual prevalence of dyspepsia.

Cholecystectomy remains the gold standard treatment for symptomatic gallstones, enabling improved general health and social activities *(24)*, despite the persistence, or the development *de novo*, of symptoms. We have shown that surgical treatment of gallstones reduces the prevalence of postcholecystectomy symptoms to levels comparable to that of a control group. Until information from prospective trials on case selection for cholecystectomy become available, clinical judgement remains the principal basis on which patients should be offered surgery for symptom relief alone.

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