

# The rising tide of cholecystectomy for biliary dyskinesia

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## SUMMARY

### Background

Expert consensus defines biliary dyskinesia as a rare disorder of the gall-bladder characterised by pain and impaired gall-bladder function.

### Aim

To determine trends in cholecystectomy rates for biliary dyskinesia in the United States.

### Methods

As biliary dyskinesia does not have a distinct diagnosis code, the narrative diagnoses for patients were reviewed and abstracted for 200 patients treated for the most commonly used diagnosis codes for biliary dyskinesia (validation sample). Time trends in cholecystectomies and hospitalisations for biliary diseases were assessed using the Nationwide Inpatient Sample (Agency for Healthcare Research and Quality) based on codes for cholecystectomy and diagnosis codes for different biliary disorders.

### Results

In the validation sample, biliary dyskinesia accounted for 81% of the patients with ICD-9 code 575.8 (*gall-bladder disease not elsewhere specified*). Between 1997 and 2010, admissions for acute cholecystitis and complications of gallstone disease decreased slightly, whereas admissions with the primary diagnosis code ICD-9 575.8 tripled. This rise was most pronounced in the paediatric population (700% increase), with biliary dyskinesia accounting for more than 10% of cholecystectomies. Compared with acute biliary diseases, significantly more of the elective hospitalisations were covered by private insurances.

### Conclusions

Practice patterns differ from expert opinion, with biliary dyskinesia accounting for an increasing fraction of cholecystectomies. The rise in these elective interventions is associated with a shift to a younger, low risk and predominantly privately insured population. Considering the benign nature of biliary dyskinesia, it is time to reassess the need for operative interventions, which have never been compared with active conservative therapy.

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## INTRODUCTION

Cholecystectomies are among the most common abdominal operations performed in the United States and European countries. Within the first decade after the advent of laparoscopic surgery, the number of operations increased significantly, mostly due to elective operations in lower risk, typically younger individuals.<sup>1, 2</sup> Gall-bladder surgery typically targeted symptomatic gallstone disease and its complications. Early studies demonstrated worse outcomes after cholecystectomy for presumed biliary problems, if no stones were found during surgery.<sup>3</sup> The reluctance to operate in the absence of morphologic gall-bladder changes changed with the introduction of functional gall-bladder imaging, which led to the description of biliary dyskinesia, defined by symptoms presumed to be biliary in nature and a low gall-bladder ejection fraction, typically assessed scintigraphically using the cholecystokin analogue sinclatide as stimulus.<sup>4-6</sup> A single randomised controlled trial demonstrated positive outcomes in all 10 patients with biliary dyskinesia treated with cholecystectomy, which contrasted with persistent symptoms in all the wait-listed persons.<sup>7</sup> While microscopic examinations of the removed gallbladders often show mild chronic cholecystitis,<sup>8</sup> the lack of severe inflammation or other complications of stone disease points at a lower risk population. The adoption of surgery as the main treatment for biliary dyskinesia is surprising, as no trial has ever compared surgery with an active intervention.

With the lowered thresholds for laparoscopic interventions, I hypothesised that biliary dyskinesia is becoming an increasingly common indication for gall-bladder surgery, especially in younger age groups. Considering the elective nature of operations for biliary dyskinesia, I also assumed that insurance coverage for patients differs from that of more urgently required operations. The specific aims for this study were to (i) determine the fraction of patients with biliary dyskinesia based on diagnostic coding, then; (ii) use this diagnostic code to assess time trends, age distribution and insurance coverage based on the Nationwide Inpatient Sample of the Agency for Healthcare Research and Quality; and (iii) compare these data for biliary dyskinesia with time trends for hospitalisations due to acute complications of cholelithiasis.

## METHODS

To test these hypotheses, the proportion of patients with biliary dyskinesia was identified based on potential diagnosis codes. Using the most appropriate diagnosis

code, time trends, age distribution and insurance coverage were determined for hospitalisations and cholecystectomies based on the Nationwide Inpatient Sample of the Agency for Healthcare Research and Quality. Biliary dyskinesia does not have a distinct code in the International Classification of Diseases (ICD). To gain insight into time trends using a data bank with hospitalisations and procedures based on ICD-9 codes, the proportion of patients with biliary dyskinesia was assessed for two different codes in a validation sample, focusing on codes that did not specifically mention the presence of gallstones, acute cholecystitis and/or obstruction. The first group was identified based on the primary billing code of 'disease of the gall-bladder not elsewhere classified' (ICD-9 code 575.8). As microscopic analyses of removed gall-bladders often show some signs of chronic cholecystitis,<sup>9-12</sup> a second group treated for 'chronic cholecystitis' (ICD-9 code 575.11) was chosen. Electronic medical records of 100 patients per group seen in the multidisciplinary Digestive Disorders Center of the University of Pittsburgh Medical Center between 1 January 2008 and 31 December 2011, were reviewed based on these primary diagnosis codes. Patient age and sex, the final descriptors of the underlying biliary disease based on the documented clinic encounter or operation, findings of ultrasound and/or computerised tomography, cholescintigraphy and histology were abstracted. The Digestive Disease Center and its affiliated clinics provide medical and surgical services for adult patients. Information about number of paediatric patients was only extracted based on the originating billing department without review of medical records or personal data. The study had been approved by the Institutional Review Board of the University of Pittsburgh Medical Center.

To estimate case volumes for the United States, Nationwide Inpatient Sample (NIS) database of the Agency for Healthcare Research and Quality was searched, using the procedural code for open (ICD-9 code 51.22) and laparoscopic cholecystectomy (ICD-9 code 51.23) and diagnoses code for cholelithiasis with cholecystitis (ICD-9 code 574.0-574.1) and acute cholecystitis (ICD-9 code 575.0-575.2) as primary reasons for hospitalisations. Incomplete cholecystectomies (ICD-9 codes 51.21 and 51.24) were not included in the analysis. Based on our validation sample, hospitalisations with the primary diagnosis of a 'not elsewhere specified disorder of the gallbladder' (ICD-9 code 575.8) were retrieved and operationally defined as hospitalisations for biliary dyskinesia.

## RESULTS

## Validation sample

Biliary dyskinesia had been diagnosed in 81 of the 100 patients identified based on the ICD-9 code 575.8. In contrast, biliary dyskinesia accounted for less than half (46%) of patients identified based on the ICD-9 code 575.11. Both groups showed a significant female predominance (Table 1). Cholelithiasis, acute cholecystitis, gall-bladder polyps, the demonstration of sludge in the gall-bladder or biliary pancreatitis were among the verbal descriptors of final diagnoses other than biliary dyskinesia. All but 17 patients (87%) with biliary dyskinesia were women with an average age of  $42.1 \pm 1.3$  years (Table 2). All patients had undergone prior imaging using ultrasound and/or CT scanning without demonstration of gallstones or signs of acute cholecystitis. In two patients, potential thickening of the gall-bladder wall had been noted. Gall-bladder function had been assessed in all, but two patients with 108 tests showing ejection fractions of less than 40% (mean  $23.5 \pm 1.8\%$ ). All but

**Table 1 |** Narrative diagnoses determined in a sample of patients selected based on the primary billing codes 575.8 (disease of gallbladder not elsewhere specified) and 575.11 (chronic cholecystitis)

	ICD-9 code 575.8	ICD-9 code 575.11
Sample size (women)	100 (women: 79)	100 (women: 83)
Age (years)	$43.9 \pm 1.5$	$43.4 \pm 2.3$
Diagnosis		
Biliary dyskinesia	81	46
Cholelithiasis	9	26
Cholecystitis	1	8
Gallbladder polyps	4	2
Sludge	2	4
Other	3	14

**Table 2 |** Clinical characteristics of patients with the narrative diagnosis of primary dyskinesia

Sample size (women)	127 (women: 112)
Age (years)	$42.1 \pm 1.3$
Symptom duration (months)	$9.3 \pm 1.5$
Gallbladder ejection fraction (%)	$23.5 \pm 1.8$
Gallbladder ejection fraction >40%	17 (13%)
Tests prior to surgery	
Number of diagnostic tests	$3.1 \pm 0.3$
CT scan	73
Ultrasound	119
Endoscopy	56

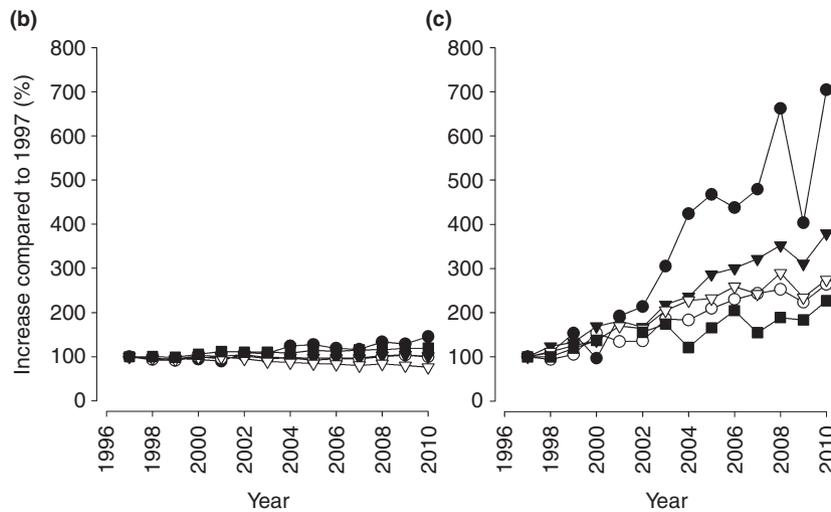
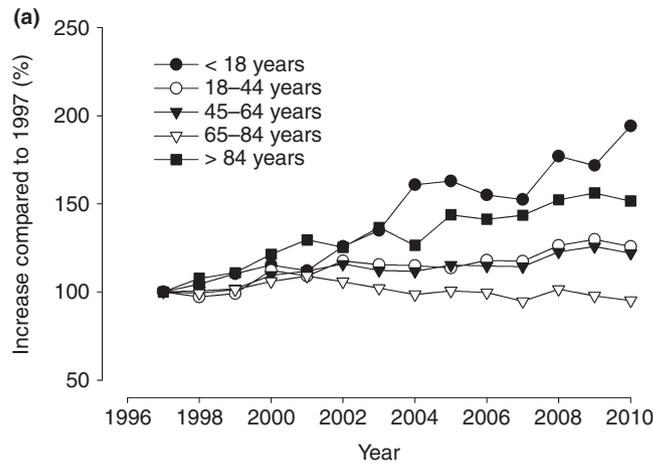
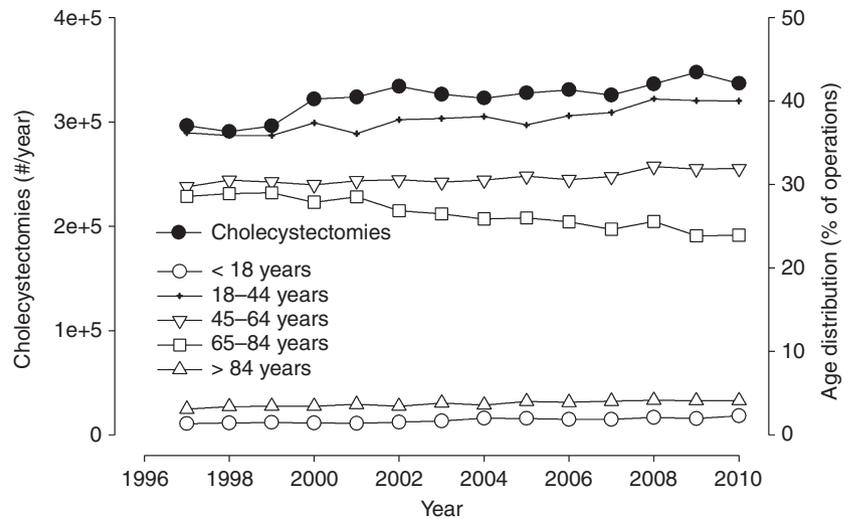
four patients with abnormal test results underwent cholecystectomy. Two patients decided against a recommended operation; in the two other cases, the physician argued for conservative management. The consulting surgeons recommended cholecystectomies in 17 patients with normal gall-bladder structure and function based on symptoms and the reproduction of pain with sinclair injection, with 16 patients consenting to the operation. Normal histological findings were seen in 23% of the removed gallbladders, 70% showed some degree of chronic inflammation with cholesterosis (5%), focal gastric metaplasia (1%) and pericholecystic fibrosis (1%) being reported in the remaining cases. Using the isolated billing codes only, paediatric physicians accounted for 16% of the claims submitted with the ICD-9 code 575.8.

## Nationwide inpatient sample

Between 1997 and 2010, the number of laparoscopic cholecystectomies increased by about 15% (Figure 1). Separating the group into different age cohorts, the majority of these surgeries was performed in young and middle-aged adults, accounting for more than 65% of the cholecystectomies (Figure 1). To examine time trends within the different age cohorts more closely, annual cholecystectomies rates were normalised to the number of operations performed in 1997. There was a shift with more operations in children and patients 85 years or older (Figure 2a). Considering the age-dependent increase in comorbidities, the percentage of inpatient deaths after laparoscopic cholecystectomy varied for the different age groups, increasing from  $0.06 \pm 0.02\%$  in patients 18–44 years of age to  $2.7 \pm 0.12\%$  in the geriatric group (mortality rates for ages 45–64 years:  $0.22 \pm 0.09\%$ ; ages 65–84 years:  $0.89 \pm 0.03\%$ ; paediatric patients: no mortality reported). To determine the reasons for this apparent shift, the age distribution was assessed for different diagnoses that represent two distinct clinical scenarios. Cholelithiasis with complicating cholecystitis (ICD-9 codes 574.0, 574.1 and 574.2) and acute cholecystitis (ICD-9 codes 575.0 and 575.1) are well-defined entities with clear diagnostic criteria, often requiring hospitalisation and early if not emergency operative interventions. In contrast, expert consensus defined biliary dyskinesia, the main diagnosis coded with the ICD-9 code 575.8, as a chronic illness,<sup>6</sup> which thus represents mostly elective interventions. There was a decrease in hospitalisations for these acute biliary disorders by about 6% (316 182/year in 1997–297 489/year in 2010); largely due to a decline in admissions in patients between 65 and 84 years (Figure 2b). Admissions in the

## Cholecystectomy for biliary dyskinesia

**Figure 1** | The plot shows the trend in annual cholecystectomies abstracted in the Nationwide Inpatient Sample (black circles) between 1997 and 2010 with changes in relative age distribution.



**Figure 2** | Change in cholecystectomy rates between 1997 and 2010. Using 1997 as baseline year, the relative changes were plotted for different age groups looking at all cholecystectomies (a) and hospitalisations for acute biliary diseases (b) or admissions with the primary diagnosis code 575.8 (c). Please see text for additional details.

paediatric and geriatric (>84 years) group rose by 45% and 19% respectively. This pattern differs strikingly from hospitalisations with not elsewhere classified disorders of the gall-bladder (ICD-9 code 575.8) as the primary diagnosis. Admissions increased about threefold (3614/year in 1997–11 189/year in 2011) with a disproportionate change in paediatric patients, where numbers rose by 700% (Figure 2c; Table 2).

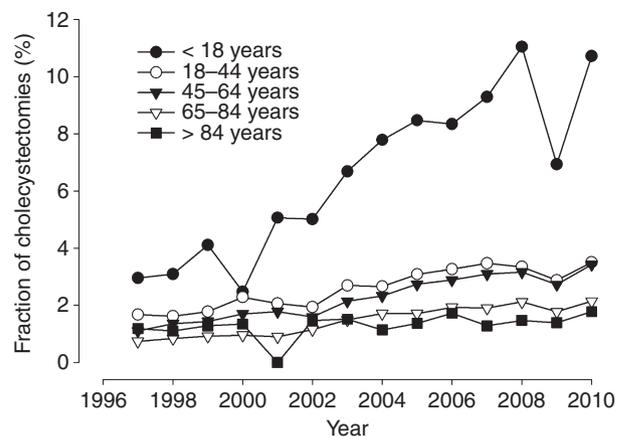
Assuming that most hospitalisations for these not otherwise specified gall-bladder disorders were associated with cholecystectomies, we next examined the relative proportion of such more elective operations. As shown in Figure 3, the ICD-9 code 575.8 accounted for less than 5% of cholecystectomies in adults, but rose from about 3–10% in the paediatric population between 1997 and 2010.

We next examined the relative representation of payers for these medical services. Medicare coverage and private insurances were responsible for close to 40% of all charges billed for cholecystectomies in 1997. There was a gradual decrease in privately insured patients with a corresponding rise on Medicaid coverage up to 2010 (Figure 4a). The same pattern emerged when we examined admissions for complications of gallstone disease or acute cholecystitis (Figure 4b). In contrast, more than half of the patients with likely biliary dyskinesia (ICD-9 code 575.8) were privately insured; with the higher number of young individuals, fewer admissions were covered by Medicare. Lastly, a significantly smaller proportion of the patients was uninsured (Figure 4c).

Considering these nationwide trends, we compared the age distribution within our validation sample with that from the overlapping time period of the Nationwide Inpatient Sample, accounting for the fraction of paediatric patients based on the billing department only (see above). As shown in Figure 5, the majority of patients fell into the ages between 18 and 64 for both data sets, although the shift to younger age groups was even more pronounced in the validation sample.

## DISCUSSION

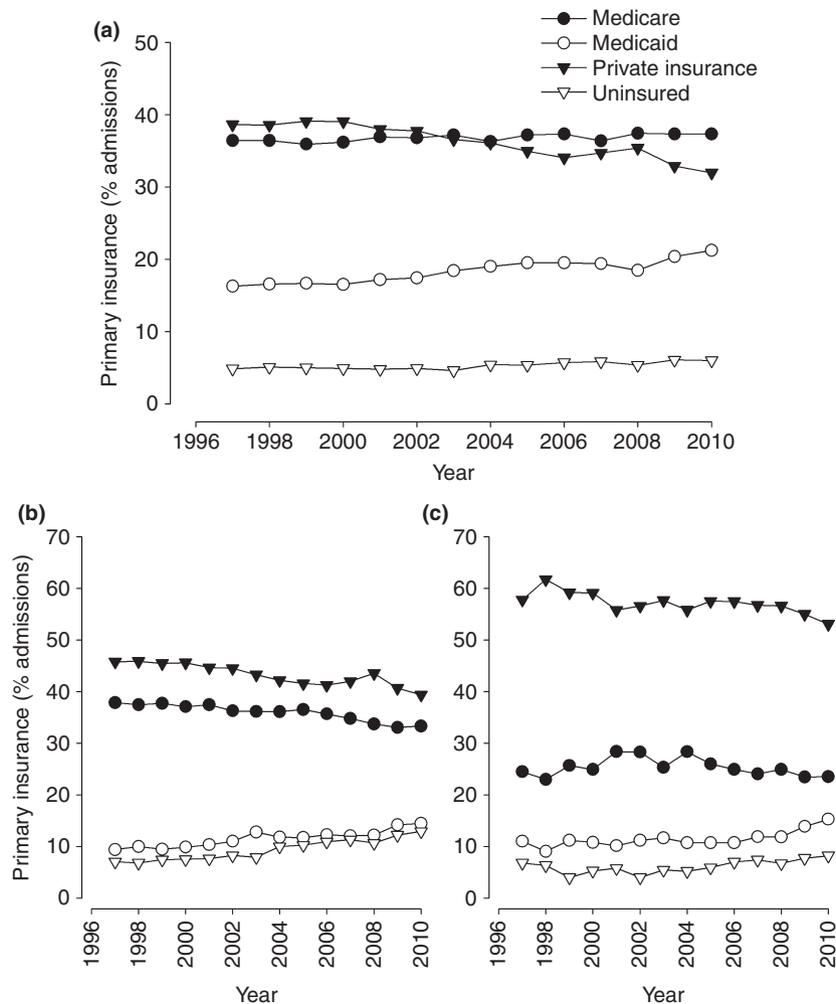
The advent of laparoscopic surgery has changed the approach to operative interventions for gall-bladder diseases. Prior studies have demonstrated an increase in cholecystectomies, mostly due to elective operations in younger patients.<sup>1, 2</sup> Our results fit into such a pattern. While numbers rose, more slowly compared to the initial years, after the adoption of laparoscopic techniques, NIS data still show an ongoing rise in cholecystectomies with a shift to younger age cohorts.<sup>13, 14</sup> Using hospitalisa-



**Figure 3** | Using hospitalisations for presumed biliary dyskinesia as a surrogate for cholecystectomies, time trends in the fraction of cholecystectomies for ICD-9 code 575.8 were determined for different age groups.

tions for biliary diseases as a surrogate for the likely indications of cholecystectomies, we noted a small decline in admissions for acute complications of biliary diseases, which stands in stark contrast with the tripling of admissions for gall-bladder diseases not elsewhere specified, a diagnostic code that is mostly used for biliary dyskinesia, as we confirmed in our validation sample. This trend was especially pronounced in the paediatric age group, where admissions likely due to biliary dyskinesia increased by about 700% within the timeframe of this study and accounted for at least 10% of the cholecystectomies. Our findings confirm on a larger scale case series from various surgical centres, listing biliary dyskinesia as the primary reason for cholecystectomy in 10–20% of adult patients<sup>13, 15–18</sup> and up to more than 50% of paediatric patients.<sup>19–22</sup> Considering expert views describing biliary dyskinesia as a rare problem,<sup>6</sup> practicing clinicians have apparently accepted this diagnosis as a relatively common problem that justifies surgical intervention.

Interestingly, there are also different patterns in insurance coverage when comparing payers for the typically more elective surgery encoded under the ICD-9 code 575.8 as opposed to the acute gall-bladder complications of stone disease. Not surprisingly, fewer admissions were covered by Medicare as younger individuals account for a larger proportion of these hospitalisations. More importantly, the more elective admissions were less often not covered by insurance with a correspondingly higher proportion of privately insured admissions. While we cannot identify the underlying reasons, this fact suggests



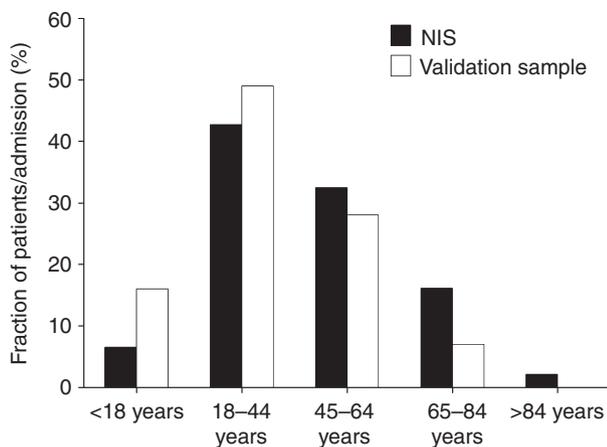
**Figure 4 |** Time trends in insurance coverage. The relative distribution of payers for all cholecystectomies (a) and hospitalisations for acute biliary diseases (b) or admissions with the primary diagnosis code 575.8 (c) was plotted for the time between 1997 and 2010.

that economic factors contribute to the decision about hospitalisation and surgery in this situation. This interpretation is indirectly supported by the relatively stable cholecystectomy rates within the nationally financed healthcare system of the Veterans Administration (VA) where insurance coverage does not seem to influence practice patterns.<sup>23</sup> Whether patients or physicians contemplate these confounders in their decisions about surgery cannot be determined using available data.

The Nationwide Inpatient Sample includes data independent of insurance coverage, age or sex and covers about 25% of all hospitalisations from all geographically distinct areas within the United States.<sup>24</sup> This rich source of information thus avoids skewing data due to tertiary referral bias or selection based on age or economic problems, such as Medicare, Medicaid or VA data. However,

it focuses by definition on hospitalisations. As more and more cholecystectomies are performed in ambulatory surgery centres, we may underestimate the true number of these interventions, especially in the low risk setting of biliary dyskinesia.

The use of a large data bank, such as the NIS, also does not enable us to clearly determine whether changes in coding are truly due to changes in diagnoses or treatments or a shift in diagnostic coding. This shortcoming is especially important, as biliary dyskinesia does not have a distinct ICD-9 code. However, during the time-frame of our study, the number of cases reported in the paediatric literature also increased, thus supporting our conclusion that operations for biliary dyskinesia have become a common practice, especially in children and adolescents.<sup>19–22</sup>



**Figure 5** | Age distribution of patients with ICD-9 code 575.8. The relative age distribution in percent was averaged for the years between 2008 and 2010 for the NIS data (black bars) and for the validation sample (white bars); information on paediatric patients in the validation sample was based billing department rather only.

We also noted an increase in cholecystectomies for patients 85 years and older. Not surprisingly, most of the operations were performed for presumably acute biliary problems and may contribute to the higher mortality rate in this subgroup. This shift may in part reflect the shifting population characteristics within the United States and lowered threshold for surgical interventions in the very elderly with the widespread availability of intensive care units and other supportive care options. In addition, it may be a consequence of a more general lowering of thresholds for surgery with the seemingly less invasive nature of laparoscopic interventions.<sup>2</sup>

The cohort of patients with biliary dyskinesia as the final diagnosis identified in our validation sample showed a female predominance with only 12% men as previously described by others.<sup>25-27</sup> Imaging studies had excluded stones or sludge within the gall-bladder in all patients. Consistent with the operational definition of biliary dyskinesia,<sup>4-6</sup> the mean gall-bladder ejection fraction was abnormal with about 20%. However, the treating physician made the diagnosis of biliary dyskinesia and suggested cholecystectomy in 13% of this cohort, even though functional gall-bladder imaging was within normal limits. The location and radiation of pain and the subjective response during sinclatide stimulation were primarily given as supporting biliary dyskinesia despite the absence of confirmed dyskinesia. While not

consistent with expert guidelines, such a practice has previously been reported in several case series, with 10%–59% of the patients with chronic symptoms and normal gall-bladder ultrasound and normal gall-bladder ejection fraction undergoing cholecystectomy.<sup>8, 9, 27-32</sup> Interestingly, outcomes after gall-bladder removal were not different when compared with patients who underwent cholecystectomy for confirmed biliary dyskinesia,<sup>8, 9, 27-32</sup> leading some surgeons to conclude that the response to the cholecystokinin (CCK) analogue is a better diagnostic criterion than the low gall-bladder ejection fraction.<sup>33</sup> Despite its apparent use in clinical practice, it is unlikely that this approach truly identifies biliary pain as CCK receptors are expressed throughout the gastrointestinal tract<sup>34-36</sup> and among other things affect colonic motility and sensory function.<sup>37, 38</sup> Based on these properties, CCK antagonists have been developed with the hope to treat common functional diseases, such as irritable bowel syndrome.<sup>37, 39</sup> In the absence of well-established data for healthy volunteers and disease controls, we may at best interpret the symptomatic response to CCK as evidence of altered sensory and/or motor function, consistent with the presence of a functional disorder of the gastrointestinal tract. However, the available data do not allow us to attribute the presence of symptoms to a single and distinct disorder, such as biliary dyskinesia.

Consistent with previously published reports,<sup>10, 11, 40</sup> evidence of chronic cholecystitis was found in about 70% of our validation sample. Such microscopic findings could potentially be seen as a surrogate marker of disease. However, several studies suggest that histological changes poorly differentiate between patients with biliary dyskinesia and asymptomatic individuals. When a systematic scoring system was used to quantify inflammatory changes within the gallbladder, no differences were found between specimens removed for biliary dyskinesia and gallbladders obtained through ‘incidental’ cholecystectomy during bariatric surgery.<sup>41</sup> Chronic cholecystitis in the absence of stone disease has been reported in up to 90% of gallbladders that were ‘incidentally’ removed during gastric bypass or other abdominal surgeries.<sup>42-48</sup> Only two autopsy studies examined the presence of inflammatory changes in the gallbladder, showing chronic acalculous cholecystitis in none of 10 paediatric, but 60.9% of 50 adult cases.<sup>49, 50</sup> Thus, the available data do not suggest that the commonly reported mild chronic acalculous cholecystitis correlates with clinically relevant symptoms or problems.

Taken together, our findings confirm a shift in cholecystectomies to a low-risk population, characterised by younger age and elective indications for surgery. In this context, biliary dyskinesia is becoming an increasingly common indication for gall-bladder surgery, especially in the paediatric group. Patterns of insurance coverage indicate that medical decision-making is influenced by socioeconomic factors. Viewed in the context of expert reviews citing the rarity of biliary dyskinesia,<sup>6</sup> we should re-evaluate current approaches to patients with presumed biliary pain. The need for a critical reassessment is indirectly supported by reports of comparable results after cholecystectomy for presumed biliary pain without documented biliary dyskinesia. While the risk of surgery is relatively low, biliary dyskinesia is by definition a benign disorder. It is the only functional disease of the gastrointestinal tract treated by surgery, even though only one randomised controlled trial with a total of 21 patients

has ever been performed to assess the effect of cholecystectomy versus wait-listing.<sup>7</sup> While the trial showed superiority of the operative approach, the lack of an active intervention in the control group and the extreme response rates with 100% and 0% remain quite unusual for functional disorders. Thus, we do not only need larger trials to see whether results can be reproduced, but also appropriately designed active interventions to meet today's standards for a control group. Drawing on approaches in patients with other functional disorders of the gastrointestinal tract, such as functional dyspepsia, we should develop and apply some of the conservative treatment strategies and test those against the current approach, cholecystectomy.

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