

# Symptomatic Cholelithiasis: A Different Disease in Men?

John C. Russell, M.D.,\* Stephen J. Walsh, Sc.D.,† Lori Reed-Fourquet, M.S.,‡  
Angela Mattie, M.P.H.,‡ and John Lynch, M.P.H.,‡ for the Connecticut Laparoscopic  
Cholecystectomy Registry

*From the Connecticut Society of American Board Surgeons,\* the Department of  
Community Medicine and Health Care, University of Connecticut School of Medicine,† and  
the Connecticut Hospital Research and Education Foundation,‡ Wallingford, Connecticut*

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## Objective

To determine the importance of gender in the clinical presentation and subsequent clinical outcome (risk of conversion from laparoscopic to open technique and risk of postoperative mortality) for patients undergoing cholecystectomy.

## Summary Background Data

Age and clinical presentation have consistently been found to be important predictors of cholecystectomy outcomes; male gender has been cited in disparate studies as possibly having prognostic significance.

## Method

A statewide cholecystectomy registry (30,145 cases between 1989–1993) was analyzed. Hierarchical log-linear modeling was used to identify associations between characteristics of clinical presentation. Multivariate logistic regression analysis was used to determine predictions of conversion and mortality.

## Results

Male gender was associated with twice the expected incidence of acute cholecystitis and pancreatitis in the elderly ( $\geq 65$  years). Males had a significantly increased risk for conversion to open technique, but this decreased during the time frame of the study. Mortality was twice as high among males (confidence interval, 1.4–2.9,  $p = 0.0001$ ).

## Conclusions

Males presenting for cholecystectomy are more likely to have severe disease. Independent of clinical presentation, they face increased risks of conversion to open technique and of postoperative mortality.

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Age has long been recognized as an important variable in predicting patient outcomes after cholecystectomy because of the increased incidence of complicated biliary

tract disease and the increased morbidity and mortality of surgery in the elderly. Less attention has been focused on the role of gender or on the possible interaction of age and gender with the clinical presentation and the clinical outcome of patients with symptomatic gallstone disease.

The Connecticut Laparoscopic Cholecystectomy Registry (CLCR) was established in 1991 to follow prospectively the clinical and economic outcomes of laparoscopic

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Address reprint requests to John C. Russell, M.D., Chief of Surgery,  
New Britain General Hospital, 100 Grand St., New Britain, CT  
06050.

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cholecystectomy.<sup>1-4</sup> This database was used to evaluate the effects of gender on the clinical indication for cholecystectomy, on the risk of conversion from laparoscopic to open surgical technique, and on the in-hospital mortality for cholecystectomy by either technique.

## PATIENTS AND METHODS

The methodology for data collection by the CLCR has been previously described.<sup>1</sup> All patients who underwent laparoscopic cholecystectomy from May 1, 1990, through September 30, 1993, and open cholecystectomy from October 1, 1988, through September 30, 1993, in an acute care, nonfederal Connecticut hospital were included in this study. Case exclusions were cholecystectomies performed because of trauma, cholecystectomies performed in association with simultaneous abdominal operations, cholecystectomies with pancreatic or biliary malignancies, and cholecystectomies performed for miscellaneous indications. The remaining cases were classified into three diagnostic categories: biliary colic-chronic cholecystitis ("colic"), acute cholecystitis ("acute"), or gallstone pancreatitis ("pancreatitis"). Cases were classified according to the form of cholecystectomy performed: laparoscopy, open surgery, or conversion. Conversions were cases in which cholecystectomies were initiated laparoscopically but were converted to open surgery. Demographic data regarding patient gender and age were also available.

To investigate relations between gender, age, and diagnosis, hierarchic log-linear modeling was used to test all two- and three-way associations. Tests were performed using a 5% level of significance. Identified associations were represented by comparing the observed number of cases in each gender-age-diagnosis combination to expected counts determined under an assumption that all three factors are independent. Confidence levels for ratios of observed-to-expected counts were calculated using the method of Byer, as described by Breslow and Day.<sup>5</sup>

Rates of intraoperative conversion from laparoscopic to open cholecystectomy were estimated relative to each category of gender, age, diagnosis, and year of treatment. The degree to which these factors predict conversion was evaluated by multivariate logistic regression. A backward stepwise algorithm that incorporated main effects based on gender, age, diagnosis, year of treatment, and all two-way interactions between these variables was applied. Factors were retained in the regression model only if they achieved statistical significance at the 5% level or if they contributed to the definition of a significant interaction term.

In-hospital mortality was defined as death in a hospital setting within 30 days of cholecystectomy, or death beyond 30 days if it occurred during the same hospitalization as the cholecystectomy. Mortality rates were deter-

**Table 1. DISTRIBUTION OF CHOLECYSTECTOMIES BY GENDER, AGE, AND DIAGNOSIS (N = 30,145)**

	Frequency	%
Gender		
Female	21,562	72
Male	8583	28
Age (yr)		
<65	21,635	72
65-79	6770	22
≥80	1740	6
Diagnosis		
Colic	19,944	66
Acute	7803	26
Pancreatitis	2398	8

mined for each category of gender, age, diagnosis, surgical procedure, and year of treatment. Relations between mortality and these factors were investigated using logistic regression models. The modeling strategy was identical to that described for the analysis of conversion rates.

All statistical analyses were performed using SPSS statistical software (SPSS, Chicago, IL).

## RESULTS

Between October 1, 1988, and September 30, 1993 (FY 1989-1993), 34,490 cholecystectomies were performed in Connecticut. Excluding 4345 patients with multiple simultaneous abdominal procedures, trauma, cholecystectomy in association with malignancy, or cholecystectomy performed for miscellaneous indications, 30,145 cases were available for analysis. The distributions of these cases relative to gender, age, and diagnosis are summarized in Table 1.

In log-linear modeling, each two-way association between gender, age, and diagnosis was statistically significant, with a *p* value < 0.0001. Ratios of observed-to-expected counts (Table 2) imply that the acute cholecystitis and pancreatitis diagnoses in older males (65-79 and ≥80) were twice as prevalent as would be expected if gender, age, and diagnosis were independent. Pancreatitis was also almost twice as common as expected in elderly females (≥80). Excess prevalence of the biliary colic-chronic cholecystitis diagnosis was associated with younger females (<65), as opposed to older females or males of any age.

Laparoscopy was the intended treatment for 50.5% of patients in this cohort. However, of the 15,215 planned laparoscopies, 785 (5.2 per 1000) were converted to open surgery after laparoscopy was initiated. Crude conversion rates (Table 3) were higher in males, in the elderly, and in patients with acute cholecystitis or pancreatitis. The

**Table 2. RATIOS OF OBSERVED-TO-EXPECTED CHOLECYSTECTOMIES BY GENDER, AGE, AND DIAGNOSIS\***

Age (yr)	Colic			Acute			Pancreatitis		
	O	O/E	95% CI	O	O/E	95% CI	O	O/E	95% CI
Females									
<65	12,276	1.2	(1.18, 1.22)	3243	0.8	(0.78, 0.84)	886	0.7	(0.67, 0.77)
65-79	2472	0.8	(0.74, 0.80)	1094	0.9	(0.82, 0.93)	451	1.2	(1.07, 1.28)
≥80	521	0.6	(0.58, 0.69)	440	1.4	(1.24, 1.50)	179	1.8	(1.55, 2.09)
Males									
<65	3115	0.76	(0.74, 0.79)	1644	1.0	(0.98, 1.08)	471	1.0	(0.88, 1.05)
65-79	1326	1.0	(0.98, 1.10)	1104	2.2	(2.08, 2.35)	323	2.1	(1.88, 2.35)
≥80	234	0.7	(0.63, 0.81)	278	2.2	(1.92, 2.44)	88	2.2	(1.79, 2.75)

O = observed count; O/E = ratio observed and expected counts; 95% CI = 95% confidence interval for the ratio of observed-to-expected counts.

\* Expected counts were calculated under the assumption that gender, age, and diagnosis are independent factors. If the independence assumption is true, the ratios should be close to 1. Ratios larger or smaller than 1 point to associations between specific categories of the gender, age, and diagnosis factors.

conversion rate was 45.5 per 1000 in 1990, the first year that laparoscopies were performed. The rate rose to 69.4 per 1000 in 1991 and dropped the following 2 years. By 1993, the conversion rate was lower (31.7 per 1000) than it initially was in 1990.

After September 30, 1991, unique CPT-4 code numbers (49310 and 49311) were introduced for laparoscopic cholecystectomy (alone, and with cholangiography). An untoward consequence was that the submission by the participating hospitals of data sheets supplementing the discharge abstracts and Medicare uniform billing (UB 82)

data decreased, making differentiation of conversions from open cholecystectomies more difficult. This may have resulted in underreporting of conversions (*i.e.*, incorrectly coding these cases as open procedures, rather than conversion cases) in FY 1992 and FY 1993. This should not have influenced the gender distribution of open and conversion cases.

Multivariate logistic regression confirmed that gender, age, diagnosis, and year of treatment were all significantly predictive of conversion (Table 4). Increasing age and the acute and pancreatitis diagnoses were associated with

**Table 3. CONVERSION RATES FROM LAPAROSCOPY TO OPEN SURGERY BY GENDER, AGE, DIAGNOSIS, AND YEAR OF TREATMENT**

	Attempted Laparoscopy	Conversions	Rate/1000
Gender			
Females	11,422	465	40.7
Males	3793	320	84.4
Age (yr)			
<65	11,830	490	41.4
65-79	2878	234	81.3
≥80	507	61	120.3
Diagnosis			
Colic	11,407	398	34.9
Acute	2916	331	113.5
Pancreatitis	892	56	62.8
Treatment year			
1989	0	0	—
1990	242	11	45.5
1991	4220	293	69.4
1992	5424	312	57.5
1993	5329	169	31.7

**Table 4. FACTORS PREDICTIVE OF CONVERSION FROM LAPAROSCOPIC TO OPEN SURGERY IN MULTIVARIATE LOGISTIC REGRESSION**

Factor	Odds Ratio	95% Confidence Interval	p
Age (yr)			
<65	1.0	—	<0.0001
65-79	1.8	(1.5, 2.1)	
≥80	2.9	(2.1, 3.8)	
Diagnosis			
Colic	1.0	—	<0.0001
Acute	3.5	(3.0, 4.1)	
Pancreatitis	1.7	(1.3, 2.3)	
Gender-year interaction			
Female 1990	1.0	—	0.03
Female 1991	2.4	(0.9, 6.5)	
Female 1992	1.5	(0.6, 4.1)	
Female 1993	0.9	(0.3, 2.5)	
Male 1990	9.3	(2.6, 33.7)	
Male 1991	4.0	(0.8, 20.7)	
Male 1992	3.2	(0.6, 16.4)	
Male 1993	1.4	(0.5, 3.8)	

**Table 5. MORTALITY FOLLOWING CHOLECYSTECTOMY BY GENDER, AGE, DIAGNOSIS, SURGICAL PROCEDURE, AND YEAR OF TREATMENT**

	Total Cholecystectomies	Death	Rate/1000
Gender			
Female	21,562	58	2.7
Male	8583	72	8.4
Age (yr)			
<65	21,635	17	0.8
65-79	6770	50	7.4
≥80	1740	63	36.2
Diagnosis			
Acute	7803	56	7.2
Colic	19,944	47	2.4
Pancreatitis	2398	27	11.3
Surgical procedure			
Laparoscopy	14,430	16	1.1
Open surgery	14,930	114	7.6
Conversion	785	0	0
Year of treatment			
1989	5045	32	6.3
1990	5341	23	4.3
1991	6582	20	3.0
1992	6679	30	4.5
1993	6498	25	3.8

higher rates of conversion. Male gender was also predictive of conversion, but its effect varied with year of treatment. During the initial year that laparoscopy was offered, conversion rates were nine times higher in males. Although this fell in subsequent years, male conversion rates continued to be higher than female conversion rates.

A total of 130 patients died after cholecystectomy, yielding a total, unadjusted mortality rate of 4.3 per 1000 cases. Crude mortality rates (Table 5) were higher among males, among the elderly (males and females), in patients with acute cholecystitis and pancreatitis, and among patients for whom open surgery was the intended technique. Perhaps because of the small number of cases, no deaths were observed among patients who were converted intraoperatively from laparoscopy to open surgery. There was no consistent pattern in mortality rates relative to year of treatment.

In the regression analyses of mortality rates, the cases that were converted from laparoscopy to open surgery were combined with the open surgery group. Because no deaths were observed among the converted cases, an odds ratio could not be estimated for that group in comparison to the group with completed laparoscopies. However, because the converted cases actually received cholecystectomy via open surgery, they were combined with the open surgery group. This permitted analysis of mortality in the complete patient cohort, but may imply slight underesti-

mation of the odds ratio for open surgery relative to laparoscopy.

In the logistic regression analysis of mortality (Table 6), gender, age, and diagnosis were all predictive of death after cholecystectomy. Year of treatment was not identified as a significant predictor. The effect of male gender was to double the risk of postoperative death. Increasing age was associated with a less favorable prognosis, especially ages ≥80. Acute cholecystitis and pancreatitis diagnoses were also related to higher mortality rates. However, age modified the effects of the diagnosis categories. Specifically, pancreatitis in patients <65 and 65 to 79 was very strongly associated with mortality, more so than the other diagnoses in those age groups and differentially from its effect in patients ≥80.

**DISCUSSION**

Although epidemiologic studies can demonstrate only association, not causation, the role of male gender demonstrated in this study in predicting operative findings and subsequent patient outcomes after cholecystectomy has important therapeutic implications. Being male and >65 is associated with more serious disease. Controlling for both age and diagnosis, males face a greater risk of conversion from laparoscopic to open surgical techniques. In addition, when controlling for age, diagnosis, and surgical procedure, males face a greater risk of death after chole-

**Table 6. FACTORS PREDICTIVE OF MORTALITY FOLLOWING CHOLECYSTECTOMY IN MULTIVARIATE LOGISTIC REGRESSION**

Factor	Odds Ratio	95% Confidence Interval	p
Gender			0.0001
Female	1.0	—	
Male	2.0	(1.4, 2.9)	
Actual surgical procedure			<0.0001
Laparoscopy	1.0	—	
Open surgery	3.3	(1.9, 5.7)	
Age-diagnosis interaction			0.01
<65 yr			
Colic	1.0	—	
Acute	2.3	(0.7, 8.0)	
Pancreatitis	11.8	(3.7, 37.3)	
65-79 yr			
Colic	13.1	(4.9, 35.2)	
Acute	15.3	(5.6, 41.6)	
Pancreatitis	28.1	(9.6, 81.6)	
≥80 yr			
Colic	68.2	(25.6, 181.4)	
Acute	83.0	(31.9, 216.2)	
Pancreatitis	69.3	(22.9, 210.0)	

cystectomy. These increased risks for males are not explained by their ages, diagnoses, or the surgical procedures they undergo. Possible gender differences in patient comorbidities such as cardiac and pulmonary disease could contribute to these mortality differences, but this issue cannot be resolved through our database. Nevertheless, from the surgeon's perspective, we believe symptomatic cholelithiasis should be considered a different, more virulent disease in male patients.

The higher morbidity and mortality of biliary tract surgery in the elderly have long been recognized.<sup>6-12</sup> In an analysis of mortality within 6 months of cholecystectomy, performed in conjunction with the National Halothane Study,<sup>10</sup> the mortality rate was approximately 5 times greater in patients age 50 to 69 than in younger patients. In both age categories, however, men had essentially twice the risk of death after cholecystectomy than women. The relative contribution of factors such as potential gender differences in patient comorbidities (*e.g.*, cardiac and pulmonary disease) and the severity of biliary disease at the time of surgery was not addressed.

Male patients appear to be at special risk for severe acute disease, with increased operative mortality. In MacDonald's<sup>13</sup> study of 500 patients undergoing cholecystectomy, 76% of patients were female. Within the acute cholecystitis subset, however, only 57% were female. In the series by Glenn and Dillon,<sup>7</sup> men represented only 39.1% of the patient population, but 60% of the patients who died. They cited this as evidence that the clinical course of acute cholecystitis is more fulminant in men. Most recently, Koo and Thirlby<sup>14</sup> reported that although only 25% of elective cholecystectomies in their institution were males, 48% of their patients with acute cholecystitis were males ( $p < 0.001$ ).

There is a higher incidence of acute cholecystitis and excess mortality in elderly males than females. In a study of 93 patients with acute cholecystitis, 76% of patients  $\leq 60$  were women and men made up 68% of the older patients ( $p < 0.005$ ).<sup>15</sup> Two series demonstrating the high morbidity and mortality of biliary tract surgery in the elderly involve largely male VA patient populations.<sup>16,17</sup> Morrow et al.<sup>16</sup> found the clinical presentation of men  $>60$  with acute cholecystitis deceptively benign: more than one third of these patients were afebrile, more than one third had a leukocyte count  $<10,000$ , and more than one fourth had no abdominal tenderness. Thirty-eight of 39 patients failed medical therapy and required surgery during that hospital admission. In Wilson et al.'s study,<sup>17</sup> a high incidence of gangrenous cholecystitis was identified among VA patients undergoing urgent or emergent cholecystectomy. The initial vital signs, physical findings, leukocyte counts, and other laboratory studies did not reliably identify patients with gangrenous change at the time of surgery. In Margiotta et al.'s study<sup>18</sup> of patients  $>70$  undergoing cholecystectomy, men had a mortality rate of

10% versus 3% for women; 54% of biliary surgery in men was done on an emergent basis (12% mortality) versus only 36% for women (7% mortality). Like Glenn and Dillon,<sup>7</sup> Margiotta et al. state that acute cholecystitis is often more fulminant in men than in women and speculate that the higher mortality rate may reflect an unwillingness of male patients to seek medical attention until their disease is well advanced. Especially in the elderly, Margiotta et al. recommend a more aggressive management approach to gallstone disease in men, intervening before the need for emergency surgery.

In addition to an increased incidence of acute pathology and an increased risk of postoperative death, a final piece of evidence supporting an actual difference between men and women in the natural history of gallstones is a higher rate of conversion from laparoscopic to open surgical technique among men.<sup>19,20</sup> Conversion from laparoscopic to open technique most frequently occurs because of severe local inflammation or scar formation distorting the anatomy of the gallbladder and the porta hepatis, precluding the safe performance of laparoscopic cholecystectomy.<sup>1</sup> Often these findings are unanticipated—that is, if the surgeon had accurately predicted the severity of disease preoperatively, the procedure would have been scheduled as an open cholecystectomy.

Sanabria et al.<sup>21</sup> comment that the surgeons in their series were often surprised by the severity of disease encountered at the time of surgery in male patients. They speculate that men may seek or follow medical advice (*i.e.*, referral for surgery) less often than women, or that there may be a difference in the disease pattern for men. Presumably, preoperative history, physical examination, and laboratory studies less reliably predict severe disease in men than in women. Possible gender-based differences in pain thresholds, body fat distribution, or other anthropomorphic differences (*e.g.*, shielding of the gallbladder by the liver from the anterior abdominal wall) could affect the accuracy of preoperative physical examination, but such factors are unexplored by the literature and by this series.

In our series, a gender difference in the conversion rate has persisted over time, although the overall conversion rates for men and women have decreased. With greater experience, surgeons are more successful in performing difficult cholecystectomies laparoscopically. Of interest, the rate of open cholecystectomies among men increased slightly in 1993, in contrast to the continued rate of decline among women (data not shown). Perhaps surgeons are recognizing in their own clinical practices the intrinsically higher conversion rate in men, and thus are more likely to proceed directly to open cholecystectomy in their male patients.

Are the apparent gender differences in the clinical course of gallstone disease in men and women biologically determined, or do they merely reflect gender differ-

ences in patient behaviors (*e.g.*, the threshold for seeking medical care, or accepting physician recommendations for surgical intervention)? Women use all forms of health services, including hospital services, more frequently than men.<sup>21</sup> An excess of total biliary complications (in contrast to severe biliary complications) identified in women compared to men in an HMO population study was interpreted by the investigators as possibly indicating a greater willingness of women to seek medical attention for mild biliary symptoms.<sup>22</sup> Whether the gender differences are biologic, behavioral, or both, the implications for patient management should be self-evident.

Like advanced age, male gender bespeaks more severe underlying biliary tract disease in symptomatic patients seeking surgical care. The initial clinical presentation may underestimate the severity of disease in men. Prolonged trials of medical therapy (intravenous fluids, parenteral pain medications, intravenous antibiotics) may result in undue delays in needed surgical intervention, with resultant increases in patient morbidity and mortality. Five prospective randomized clinical series comparing early *versus* late cholecystectomy for acute cholecystitis have found that early surgery is associated with fewer technical complications, fewer deaths, and faster patient recovery.<sup>23</sup> Given the unfavorable natural history of symptomatic gallstone disease in men, we advocate an aggressive surgical approach, especially in the elderly.

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