12-2-2015

Gender Differences in Choice of Procedure and Case Fatality Rate for Elderly Patients with Acute Cholecystitis: A Masters Thesis

Courtney E. Collins
University of Massachusetts Medical School

GENDER DIFFERENCES IN CHOICE OF PROCEDURE AND CASE FATALITY RATE FOR ELDERLY PATIENTS WITH ACUTE CHOLECYSTITIS

A Masters Thesis Presented by

Courtney Elaine Collins MD

Submitted to the Faculty of the

University of Massachusetts Graduate School of Biomedical Sciences Worcester

In partial fulfillment of the requirements for the degree of

MASTERS OF SCIENCE

2 December 2015

Masters In Science in Clinical Investigation

Gender Differences in Choice of Procedure and Case Fatality Rate for Elderly Patients with Acute Cholecystitis

A dissertation presented by

Courtney Collins

The signatures of the Dissertation Defense Committee Signify Completion and Approval as to the style and content of the Dissertation

Heena Santry MD. MS. , Thesis Advisor

Gordon Fitzgerald PhD., Member of Committee

Robert Goldberg PhD., Member of Committee

The signature of the Chair of the Committee Signifies that the written dissertation meets the requirements of the dissertation Committee

Fred A. Anderson Jr. PhD., Chair of Committee

The Signature of the Dean Signifies that the written dissertation meets the requirements of the Dissertation Committee

Anthony Carruthers, PhD.

Dean of the Graduate School of Biomedical Sciences

Masters of Science in Clinical Investigation

Acknowledgements

There are many people I would like to thank for making this thesis possible. First to Rob Goldberg, Kate Lapane, and the entire staff at GSBS for allowing me to participate in their MSCI program and having the patience with me to see it through. Secondly I owe a major debt to my statisticians Julie Flahive and Didem Ayturk who helped me through my darkest days (and nights) of statistical analysis. Next I would not have been able to pursue my research at all without the support of Fred Anderson whose guidance and friendship have meant the world to me. Finally I owe my greatest thanks to my mentor Dr. Heena Santry. Her passion for research inspired me during my research time and I appreciate both her support and her enthusiasm for my crazy ideas more than I can say. Thank you to everyone.

Abstract

Background: Treatment decisions for elderly patients with gallbladder pathology are complex. Little is known about what factors go into treatment decisions in this population. We used Medicare data to examine gender-based differences in the use of cholecystectomy vs. cholecystostomy tube placement in elderly patients with acute cholecystitis.

Methods: We queried a 5% random sample of Medicare data (2009-2011) for patients ≥65 admitted for acute cholecystitis (by ICD-9 code) who subsequently underwent a cholecystectomy and/or cholecystostomy tube placement. Demographic information (age, race), clinical characteristics (Elixhauser index, presence of biliary pathology), and hospital outcomes (case fatality rate, length of stay, need for ICU care) were compared by gender. A multivariable model was used to examine predictors of cholecystectomy vs. cholecystostomy tube placement.

Results: Of 4063 patients admitted with cholecystitis undergoing the procedures of interest just over half (58%) were women. The majority of patients (93%) underwent cholecystectomy. Compared to women, men were younger (average age 76 vs. 78, p value <0.01) and had few comorbidities (average Elixhauser 1.2 vs. 1.4 p value <0.01). Case fatality rate was similar between men (2.5%) and women (2.4% p value 0.48). A higher percentage of men spent time in the ICU (36%) compared to women (31% p value

<0.01). On multivariable analysis men were 30% less likely to undergo cholecystectomy (OR 0.69, 95% CI 0.53-0.91).

Conclusion: Elderly men are less likely than elderly women to undergo cholecystectomy for acute cholecystitis despite being younger with less co morbidity and are more likely to spend time in the ICU. More research is needed to determine whether a difference in treatment is contributing to the higher rate of ICU utilization in elderly men with acute cholecystitis.

Table of Contents

List of Tables

Chapter I: Introduction

Gallbladder disease, including acute cholecystitis, is the most common indication for abdominal surgery in the United States.(Richter 2003, Shaffer 2006) Traditionally, treatment for acute cholecystitis is surgical removal of the gallbladder (cholecystectomy). However, patients at high risk of complications due to co-morbidities, age, or advanced disease may also be managed by antibiotics and placement of a cholecystostomy (drainage) tube to eradicate the infection. Typically surgical removal of the gallbladder is still indicated after the acute phase of the infection has cleared in patients with appropriate operative risk. Importantly, there are no explicit guidelines regarding the appropriateness of cholecystectomy vs. cholecystostomy tube placement in patients with cholecystitis. While a multitude of factors go into this treatment decision, in the end it is often left up to physicians to determine whether a patient is or is not a surgical candidate. This decision process may be especially complicated in the elderly who are at greater risk for dying after cholecystectomy(Kuy et al. 2011).

Little research has been done to determine what non-medical factors may play a role in treatment decisions for patients with acute cholecystitis, and virtually none exists with a focus on elderly patients. In particular, little is known about possible gender differences in the management of elderly patients with biliary disease. The only study to date that has examined gender differences among patients with cholecystitis found that women were more likely to undergo laparoscopic cholecystectomy, and they were operated on sooner than men(Dua et al. 2013).

Using data from a sample of Medicare beneficiaries, we examined possible gender based differences in the treatment of elderly patients with acute cholecystitis through the use of cholecystectomy vs. cholecystostomy tube placement. We also examined sex-based differences in hospital case-fatality rates (CFRs) for elderly patients with acute cholecystitis. We hypothesized that elderly men would have lower rates of cholecystectomy, but a higher odds of dying during their acute hospitalization, compared with elderly women.

Chapter II: Methods

Data Sources

Medicare Provider and Analysis Review/MEDPAR (inpatient and select outpatient) event files were queried for a random 5% sample of Medicare Beneficiaries for the years 2009-2011. Patients were included in the study if they were 65 years or older on January 1, 2009 and had at least 1 year of continuous Part A and B coverage without health maintenance organization (HMO/Part C) for any year to ensure completeness of data.

MEDPAR was used to obtain variables related to hospitalization including diagnoses (up to 10 for inpatient files, 20 for outpatient files), procedures (up to 10), need for ICU care, and length of stay (LOS) both overall and in the ICU (ICU-LOS). MEDPAR was also used to calculate each patient's Elixhauser index to characterize overall comorbidity burden(Elixhauser et al. 1998). Demographic factors (age, sex, race) were obtained from Medicare denominator files.

Case Identification

Patients were included in this study if they were admitted to acute care hospitals during the years under study with a primary diagnosis of acute cholecystitis by ICD-9 code (574.0, 574.3, 574.6, 574.8, 575.0, 575.12) and subsequently underwent a cholecystectomy (51.2x), a cholecystostomy tube placement(51.01), or both during their index admission. Only patients with an urgent/emergent admission were included in order to limit the study to patients with acute presentations of cholecystitis and exclude patients

presenting for elective cholecystectomy for previously diagnosed chronic or subacute cholecystitis. Because our primary study aim was to determine who underwent definitive treatment (i.e., cholecystectomy) during their acute hospital stay, patients undergoing cholecystectomy, and those undergoing both cholecystostomy and subsequent cholecystectomy, were included in the cholecystostomy group; those who underwent cholecystostomy tube placement alone were considered in the cholecystostomy tube group. Concomitant biliary pathology (as a secondary diagnosis) was also identified using ICD-9 codes (Appendix 1) in an attempt to characterize the severity of biliary disease. Patients with chronic cholecystitis or isolated biliary diagnoses, such as cholelithiasis or cholangitis, without a diagnosis of cholecystitis were not included. Only the first hospitalization for acute cholecystitis was considered for each patient.

Statistical Analysis

Socio-demographic (age, sex, race) and clinical characteristics (Elixhauser index, presence of concomitant biliary pathology), as well as hospital outcomes (in-hospital mortality, need for ICU care, length of stay (LOS)) were compared for men and women undergoing a procedure after being admitted urgently/emergently for cholecystitis during the years under study. Chi square tests were used to compare categorical variables, Wilcoxon rank sum tests were used for non-normally distributed continuous variables, and t-tests for differences in continous variables between men and women.

A logistic regression model was used to examine the association between gender and the odds of undergoing cholecystectomy vs. cholecystostomy tube placement only

for patients who underwent one of the two procedures., For this model , age in 10 year increments, race, Elixhauser index, concomitant biliary disease, and treatment modality (cholecystectomy vs. cholecystostomy tube placement) were included in the model. A second multivariable logistic regression model was used to analyze the effect of gender on the odds of dying during hospitalization in patients admitted with cholecystitis. The final mortality model included age in 10 year increments, gender, Elixhauser index, and treatment modality.

This study was deemed exempt by the University of Massachusetts Institutional Review board and was approved by the Center for Medicare and Medicaid Services (CMS) via RESDAC. All analyses were performed using SAS 9.2 (SAS institute, Carey NC, 2013).

Chapter III: Results

Study Population Characteristics

During the years under study, a total of 5,521 patients were admitted with acute cholecystitis, 4063 (74%) of whom underwent one of the two procedures of interest. The average age of study patients was 77.5 years, 58 % of the study sample were women, and 77 % were Caucasian (Table 1). Compared with men, women were significantly older and had a greater frequency of each of the examined comorbidities (Table 1). Women were also more likely to have cholelithiasis or other biliary pathology.

Univariate Analysis

On univariate analysis there were no differences in the rates of cholecystectomy between men and women (Table 1). Patients with cholecystitis had relatively low in-hospital CFRs, being similar in men (2.1%) and in women (2.4%). The average hospital LOS was also similar in men and women and men were significantly more likely to have been admitted to the ICU.

Multivariable Analysis

In multivariable adjusted analyses, men were approximately 30% less likely to have undergone cholecystectomy compared with women after adjusting for several potential confounding variables including age in 10 year increments, race, Elixhauser index, concomitant biliary disease, and treatment modality (OR 0.69, 95% CI 0.53- 0.91)

Despite differences in surgical management and other factors between the 2 sexes, there were men did not have a significantly higher CFRs after adjusting for age in 10 year increments, gender, Elixhauser index, and treatment modality (OR 1.04, 95% CI 0.67 - 1.61).

Chapter IV: Discussion

We found that, despite being older and having more comorbidities, elderly women were more likely than elderly men to undergo cholecystectomy after being admitted for cholecystitis. Although men more frequently required ICU care, in-hospital death rates were similar between the groups and gender was not an independent predictor of short-term mortality in multivariable adjusted analyses.

The present literature on cholecystitis largely focuses on predictors of morbidity and mortality rather than predictors of surgical management for this condition. In general, the collective results of these studies suggest that men with cholecystitis, particularly those undergoing cholecystectomy, have worse outcomes compared with women. For example, Carbonell *et al.(*Carbonell et al. 2005) used the Nationwide Inpatient Sample to examine the outcomes of patients undergoing cholecystectomy in 2000. Men admitted with cholecystitis fared significantly worse than women in terms of morbidity (15.5% with complications vs. 9.6% for women) and hospital death rates (2.2% vs. 1%). After multivariable adjustment for patient and hospital level factors, gender remained a significant predictor of morbidity, but not mortality.

Similar to the results of this study, we failed to find a difference in hospital CFRs between men and women. Men did have higher rates of ICU care on univariate analysis, despite the fact that they were younger, and had lower average co morbidity scores compared with women. Thus although we failed to observe any differences in short-term death rates between men and women, men with cholecystitis may be more likely to have

a complicated hospital stay. Whether or not this is due to underlying medical pathology or to the treatments used for the management of their acute cholecystitis is not clear from this analysis.

In examining the utilization of cholecystostomy tubes in the setting of cholecystitis, there appears to be support for the notion that men receive cholecystostomy tubes more frequently than women. In a retrospective review of over 300,000 patients in the Nationwide Inpatient Sample who had undergone treatment for acute cholecystitis from 1998-2010 (Anderson, Chang, and Talamini 2013) investigators found a significant difference in the gender makeup of patients who underwent a cholecystostomy (41% female) compared with those who underwent cholecystectomy (51% female). Similar to the study by Carbonell and colleagues, the authors did not examine the choice of cholecystostomy vs. cholecystectomy as a primary outcome and, therefore, did not examine predictors of undergoing one procedure vs. the other. They also did not report any variables related to the severity of presentation that would help discern why the choice was made between cholecystostomy and cholecystectomy. Differences in the gender distribution of the cholecystostomy tube vs. cholecystectomy group suggests, however, that there may be differences selecting a therapeutic approach for male and female patients with cholecystitis, although this is speculative without an analysis adjusting for patient and disease factors.

To date there has been only one study that examined the role of gender in the management of patients with cholecystitis. Dua *et al.*(Dua et al. 2013) used the Nationwide Inpatient Sample to examine gender differences in disease severity but also

in patterns of operative management for patients admitted with cholecystitis. These investigators found that 75% of women admitted with cholecystitis underwent a cholecystectomy during their admission compared with 70% of men. Women also had a significantly shorter time to surgery than did men (1.6 vs. 1.9 days). The authors failed to state if those not undergoing cholecystectomy received another therapeutic procedure (i.e. ,cholecystostomy tube placement) or had no treatment at all. This is important as some patients may have been very sick and required a drainage tube while others may have had self-limited cholecystitis that allowed them to be discharged on antibiotics.

Unlike the previously described studies, Dua *et al*. reported gender differences in variables such as comorbidity and admission type, and attempted to adjust for the severity of cholecystitis. The authors found that women were approximately 7 years younger, had fewer comorbidities, were more likely to be admitted non-urgently, and had less severe biliary disease than men, which could have, in part, explained differences in the use of surgery vs. cholecystostomy. . Irrespective, the results of this study imply that women are more likely than men to undergo laparoscopic cholecystectomy. Furthermore, in multivariable analysis, time to surgery (which was increased by half a day in men) was found to be a significant predictor of mortality after adjusting for a number of patient factors (including gender, age, co morbidities, and severity of biliary disease). This means that not only are men less likely to undergo cholecystectomy, the fact that they are being operated on later than women may put them at an increased risk for death.

In the present study we found that elderly men were approximately 30% less likely than women to undergo cholecystectomy during an admission for cholecystitis

after adjusting for other factors, including the presence of concomitant biliary pathology and overall comorbidity burden. Our results suggest that even though men are younger with fewer co morbidities (and arguably more appropriate surgical candidates), they are less likely to undergo the definitive surgical procedure for the management of acute cholecystitis than women. This is especially important because elderly patients are at increased risk of adverse outcomes with each episode of symptomatic biliary disease, including a 10 fold increase in mortality compared withyounger patients (Harness, Strodel, and Talsma 1986). Although the hospital death rates did not differ between men and women in the present study, the fact that men were less likely to have a cholecystectomy means that more male patients will be discharged with their gallbladder intact, leaving them at risk of having recurrent gallbladder pathology (and all associated complications) in the future.

There is support in the literature for the idea that physicians in general and surgeons in particular, may approach medical conditions differently in men vs. women. For example, it has been well documented in the cardiac literature that women with heart disease are less likely to undergo cardiac catheterization and cardiac bypass surgery than men.(Ayanian and Epstein 1991, Vaccarino et al. 2005, Wong et al. 1997) Women have also been shown to be less likely to receive a kidney than men even with similar stages of kidney disease(Kjellstrand 1988, Gaylin et al. 1993, Held et al. 1988). The reasons contributing to these differences, however, have not been extensively studied. Many physicians point to differences in patient presentation or symptoms as the driving force behind differences in the management of surgical patients. However, these differences

appear to persist even when they are accounted for in multivariable adjusted models and with simulated patients. For example, one study used standardized patients (one man, one woman) to examine the referral practices of physicians when evaluating patients with knee pain. The authors found that the male standardized patient was referred to a surgeon for management of his chronic knee pain twice as often compared with the female despite the fact that they gave identical medical histories and had identical “symptoms”(Borkhoff et al. 2008). This difference was particularly pronounced among surgeons who were 22 times more likely to recommend surgery for the male patient compared with the female patient.

The perception of “men’s diseases” and “women’s diseases” might explain why men are more likely to get surgery in some instances (heart disease) but less likely to undergo surgery in other instances (biliary disease/cholecystitis). experienced. It is possible that male patients with cholecystitis experience a delay in diagnosis because physicians simply don’t think of biliary disease when they see a male patient, even though they may have the same symptomatology as women. This delay in management could also explain the increased use of open cholecystectomy and the reports of more severe biliary disease in male patients in the aforementioned studies. Physicians may simply not recognize cholecystitis in a male patient until he is well into its clinical course whereas women are diagnosed in the more early phases of disease with less inflammation.

The published literature and our results suggest that men are not only less likely to receive a cholecystectomy in the setting of acute cholecystitis compared with women but

that they may also be at increased risk for adverse outcomes and more complicated hospital stays. Differences in surgical management of patients with other conditions suggest that there may be unconscious bias on the part of physicians when evaluating patients. Accordingly, the perception of cholecystitis as a women's disease may cause delayed diagnosis and/or treatment of male patients and could explain differences not only in the utilization of cholecystectomy but also in short-term death rates. Educating physicians about potential disparities in diagnosis and treatment of biliary disease may help improve outcomes for men with acute cholecystitis.

Our study has some important limitations to consider in the interpretation of our results. First, our study is limited to elderly patients so we are unable to comment on gender differences in the approach to acute cholecystitis in younger populations. Secondly, the use of claims data means that our results could be subject to coding errors in terms of both the diagnosis of acute cholecystitis and the procedure used. Lastly, we did not have access to any clinical data, such as laboratory values or radiology findings, which limits our ability to comment on disease severity or how unstable patients may have been when admitted. We have attempted to adjust for this by including the presence of other biliary diagnosis codes as a proxy for the severity of biliary disease, but the lack of other clinical data makes stratifying patients based on disease severity difficult.

The current study suggests that the selection of treatment for patients admitted with acute cholecystitis is influenced to a limited extent by the patient's gender. One possible area that needs future research is whether these findings are noted in younger age groups. Additionally, future research could examine whether or not men and women

who do not undergo cholecystectomy get readmitted with recurrent biliary disease, an important factor when considering the long -term management of these patients. Finally, future studies should examine the role of physician and hospital factors, such as surgeon gender and age or hospital setting, on the management of acute cholecystitis in elderly patients since these factors could also influence which patients are undergoing surgery and which are not. If men are indeed receiving suboptimal treatment of biliary disease (or women are being over treated), identifying the settings in which this is most likely to happen might allow for targeted interventions in these situations.

Table 1. Characteristics of Medicare Beneficiaries Admitted with Acute Cholecystitis and who had Cholecystectomy or Cholecystostomy Tube placement

	Male (n=1673)	Female (n=2390)	p-value
Age, mean (SD)	76 (7.2)	78 (8)	<.01
Race % (N)			**<0.01**
White	78 (1303)	77 (1844)	
Black	5.7 (95)	9 (214)	
Hispanic	12 (197)	10 (238)	
Asian	2.9 (49)	2.9 (68)	
Other	1.7 (29)	1.1 (26)	
Elixhauser Index, mean (SD)	1.2 (2.1)	1.4 (2.3)	<0.01
Biliary diagnoses % (N)			
Cholangitis	6 (101)	5.7 (137)	0.68
Gallstone pancreatitis	13 (224)	15 (360)	0.13
Cholelithiasis	77 (1292)	80 (1917)	0.02
Other	7.8 (131)	9.8 (234)	0.03
Treatment group % (N)			**0.14**
Cholecystectomy	93 (1553)	94 (2246)	
Cholecystostomy	7.2 (120)	6 (144)	
Hospital Outcomes			
Case Fatality Rate % (N)	2.1 (35)	2.4 (58)	0.48
Median LOS *(IQR)	6 (4, 9)	6 (4, 9)	0.68
ICU stay % (N)	36 (600)	31 (731)	<0.01

*out of survivors (N= 3970)

Appendix: ICD-9 code for cholecystitis and concomitant biliary pathology

Condition	ICD-9 code
Acute Cholecystitis	574.3, 574.0, 574.6, 574.8, 575.0, 575.12
Cholelithiasis	574.x
Cholangitis	576.1
Gallstone pancreatitis	577.0
Other biliary diagnosis	575.2-6; 575.8-575.9; 576.2-576.5; 575.8-575.9

Bibliography

Anderson, J. E., D. C. Chang, and M. A. Talamini. 2013. "A nationwide examination of outcomes of percutaneous cholecystostomy compared with cholecystectomy for acute cholecystitis, 1998-2010." *Surg Endosc* no. 27 (9):3406-11. doi: 10.1007/s00464-013-2924-5.

Ayanian, J. Z., and A. M. Epstein. 1991. "Differences in the use of procedures between women and men hospitalized for coronary heart disease." *N Engl J Med* no. 325 (4):221-5. doi: 10.1056/NEJM199107253250401.

Borkhoff, C. M., G. A. Hawker, H. J. Kreder, R. H. Glazier, N. N. Mahomed, and J. G. Wright. 2008. "The effect of patients' sex on physicians' recommendations for total knee arthroplasty." *CMAJ* no. 178 (6):681-7. doi: 10.1503/cmaj.071168.

Carbonell, A. M., A. E. Lincourt, K. W. Kercher, B. D. Matthews, W. S. Cobb, R. F. Sing, and B. T. Heniford. 2005. "Do patient or hospital demographics predict cholecystectomy outcomes? A nationwide study of 93,578 patients." *Surg Endosc* no. 19 (6):767-73. doi: 10.1007/s00464-004-8945-3.

Dua, A., A. Dua, S. S. Desai, S. Kuy, R. Sharma, S. E. Jechow, J. McMaster, B. Patel, and S. Kuy. 2013. "Gender based differences in management and outcomes of cholecystitis." *Am J Surg* no. 206 (5):641-6. doi: 10.1016/j.amjsurg.2013.07.011.

Elixhauser, A., C. Steiner, D. R. Harris, and R. M. Coffey. 1998. "Comorbidity measures for use with administrative data." *Med Care* no. 36 (1):8-27.

Everhart, J. E., M. Khare, M. Hill, and K. R. Maurer. 1999. "Prevalence and ethnic differences in gallbladder disease in the United States." *Gastroenterology* no. 117 (3):632-9.

Gaylin, D. S., P. J. Held, F. K. Port, L. G. Hunsicker, R. A. Wolfe, B. D. Kahan, C. A. Jones, and L. Y. Agodoa. 1993. "The impact of comorbid and sociodemographic factors on access to renal transplantation." *JAMA* no. 269 (5):603-8.

Harness, J. K., W. E. Strodel, and S. E. Talsma. 1986. "Symptomatic biliary tract disease in the elderly patient." *Am Surg* no. 52 (8):442-5.

Held, P. J., M. V. Pauly, R. R. Bovbjerg, J. Newmann, and O. Salvatierra, Jr. 1988. "Access to kidney transplantation. Has the United States eliminated income and racial differences?" *Arch Intern Med* no. 148 (12):2594-600.

Kjellstrand, C. M. 1988. "Age, sex, and race inequality in renal transplantation." *Arch Intern Med* no. 148 (6):1305-9.

Kuy, S., J. A. Sosa, S. A. Roman, R. Desai, and R. A. Rosenthal. 2011. "Age matters: a study of clinical and economic outcomes following cholecystectomy in elderly Americans." *Am J Surg* no. 201 (6):789-96. doi: 10.1016/j.amjsurg.2010.04.018.

Richter, J. E. 2003. "The enormous burden of digestive diseases on our healthcare system." *Curr Gastroenterol Rep* no. 5 (2):93-4.

Shaffer, E. A. 2006. "Gallstone disease: Epidemiology of gallbladder stone disease." *Best Pract Res Clin Gastroenterol* no. 20 (6):981-96. doi: 10.1016/j.bpg.2006.05.004.

Vaccarino, V., S. S. Rathore, N. K. Wenger, P. D. Frederick, J. L. Abramson, H. V. Barron, A. Manhapra, S. Mallik, H. M. Krumholz, and Investigators National Registry of Myocardial Infarction. 2005. "Sex and racial differences in the

management of acute myocardial infarction, 1994 through 2002." *N Engl J Med* no. 353 (7):671-82. doi: 10.1056/NEJMsa032214.

Wong, C. C., E. S. Froelicher, P. Bacchetti, H. V. Barron, L. Gee, J. V. Selby, R. Lundstrom, B. Swain, and A. Truman. 1997. "Influence of gender on cardiovascular mortality in acute myocardial infarction patients with high indication for coronary angiography." *Circulation* no. 96 (9 Suppl):II-51-7.