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Gender as a predictive factor in cholecystectomy — is it true or false?

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Abstract: Introduction: Cholecystolithiasis is one of the most frequent disorders of the human digestive system in a present population. It is common to point out that male gender is one of strong risk factors for complications during cholecystectomy, however the debate about that seems to be still open.
Aim of the study: The aim of this study was to compare the values related to the course and treatment effects between gender in patients undergoing cholecystectomy, based on own material.
Materials and Methods: The study encompassed 504 patients who were admitted to General Surgery And Polytraumatic Injury Department of University Hospital in Kraków, Poland between 2013 and 2018, with the initial diagnosis of cholecystolithiasis (scheduled cases) and acute cholecystitis (emergency cases). The patients underwent surgical gallbladder removal. In this group there were 326 (64.7%) female and 178 (35.3%) male patients.
Results: Statistically significant differences between both genders were found containing age, type of admission, numeric rating scale of pain during admission, results in American Society of Anesthesiologists physical status classification system, outcomes in Acute Physiology And Chronic Health Evaluation II severity-of-disease classification system, percentage of conversions, mortality, period of time from admission to surgical procedure, mean duration of the procedure, blood tests and histopathological results.
Conclusions: Subgroups of the cases where determining factor is gender are strongly heterogeneous. Although treatment results were different for both subgroups and these differences were partly statistically significant, it cannot be clearly determined on the basis of a study with such selection of patients, that gender is an independent risk factor for surgical gallbladder removal.

Keywords: gender, cholecystectomy, acute cholecystitis, chronic cholecystitis, gallbladder, cholecystolithiasis.

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Introduction

Cholecystolithiasis is one of the most frequent disorders of the human digestive system in a present population. According to epidemiological studies, the disease occurs in about 10–20% of adults and is 2–3 more frequent in females [1, 2]. The very first of formally reported, surgical gallbladder removal was made by dr. Carl Johann August Langenbuch in Saint Lazarus Hospital in Berlin, Germany at 15th July 1882 [3]. French surgeon Mouret is widely known as the first performer of laparoscopic cholecystectomy in March 1987. However, the true first surgeon who did this laparoscopic procedure was Mühe from Germany, who presented that during the Congress of the German Surgical Society in April 1986 [4–6]. Nowadays the laparoscopic cholecystectomy is the gold standard in patients who require gallbladder removal. There is a strong widespread belief that the cholecystectomy in males, both laparoscopic and open, is remarkably more difficult to perform and comes with more serious subsequent complications during postoperative period. There are plenty of publications investigating or even confirming this conviction with hypotheses to prove that [7–11]. However, there is no single article proving that this may be related to anatomical variants associated with gender [12–15].

Aim of the study

The aim of this study was the assessment whether the process and outcomes of the cholecystectomy as a type of treatment is related to patients' gender. Furthermore the study was made to focus on hypothetical predisposing factors connected with gender leading to changes in period of that kind of treatment.

Materials and Methods

The study encompassed patients admitted to General Surgery, Orthopedics And Polytraumatic Injury Department of University Hospital in Kraków, Poland between years 2013–2018. These patients were qualified to scheduled or emergency cholecystectomy subsequently to past medical history, physical examination and ultrasound tests according to Tokyo criteria [16, 17]. In one single case there was ultrasound-guided cholecystostomy performed due to critical medical status of female patient disqualifying her from any more advanced surgical procedures. The cases were subsequently divided into two subgroups in terms of their gender — 326 females and 178 males. This was a prospective study. Data processing was based on Microsoft Excel. The statistics were performed using Student's T test of difference between means in terms of different variances, chi-squared test and chi-squared test with Yates's correction for continuity [18]. The comparison between the quantity overall of both subgroups was

made considering type of admission (emergency or scheduled), mean age, type of pain — colic or constant, duration of pain, numeric rating scale (NRS) of pain during admission, subjective pain location [19]. The cases were compared using results in American Society of Anesthesiologists physical status classification system (ASA) [20]. Physical examination outcomes of abdominal cavity were assessed, including the shape of abdomen in supine position, location of soreness during palpation, rebound tenderness. The average values of chosen blood test results, and outcomes in Acute Physiology And Chronic Health Evaluation II severity-of-disease classification system (APACHE II) were both calculated [21]. Average period of time from admission to start of surgical procedure, average length of hospital stay, average duration of the surgery, percentage of surgical types of the procedure including conversion, were all compared. The intraoperative diagnosis made by surgeons, histopathological results (including length of dissected gallbladder), postoperative complications, amount of patients who were treated in intensive care unit (ICU) postoperatively and mortality in both subgroups were also compared.

Results

504 patients underwent surgical gallbladder removal including scheduled cases with diagnosis of cholecystolithiasis and emergency ones because of acute cholecystitis. This group included 326 (64.7%) female and 178 (35.3%) male patients, mean age was 54.8 (SD 16.96) years old. Surgical procedures applied in those cases were: laparoscopic cholecystectomy (n = 450, 89.3%), laparoscopic cholecystectomy converted to open cholecystectomy (n = 35, 6.9%), open cholecystectomy (n = 18, 3.6%), ultrasound guided cholecystostomy (n = 1, 0.2%). Mean hospital stay was 84.9 (SD 78.26) hours. Mean period of time from admission to start of surgical procedure was 15.5 (SD 24.36) hours. Mean duration of surgical procedure was 83.7 (SD 42.83) minutes. Postoperative complications occurred in 65 (12.9%) cases, therein surgical (n = 36, 7.1%) and non-surgical (n = 29, 5.8%). 14 (2.8%) patients were transmitted to ICU during postoperative period. Mortality was 11 (2.2%) cases, wherein 10 of them died during ICU stay.

Female subgroup

The study consisted of 326 female patients with mean age of 52.4 (SD 16.12) years old. Scheduled cases were 198 (60.8%), whereas 128 (39.2%) were emergency ones. Average period of time from start of pain to admission was 10.4 (SD 13.65) days. Duration of symptoms in these patients was: 0–24 hours in 12.7% of the cases, 2–7 days in 26.9%, 2–4 weeks in 9.6%, 2–12 months in 33.5%, 2 or more years in 17.3% of them. Pain was described as constant in 41.8% of the cases, or colic in 58.2%. Subjective pain

location was: below right costal arch in 81.7%, epigastrium in 16.2%, whole abdomen in 2.1%. Pain severity measured with NRS was in mean 3.2 (SD 3.03). Physical status in accordance with ASA was evaluated as: ASA I — n = 217, 66.6%; ASA II — n = 56, 17.2%; ASA III — n = 43, 13.2%; ASA IV — n = 10, 3.1%. Abdominal cavity during supine position was: distended in 35.6%, scaphoid in 8.1%, and flat in 56.4%. Sore tenderness investigated during admission was: below right costal arch in 84.5% of the cases, in epigastrium in 9%, the whole abdomen in 6%. Muscle guarding was in 72.8% of the patients, and rebound tenderness was in 7.7% of them. The mean results of the blood test outcomes such as white blood cells count (WBC), the hematocrit (Hct), the average volume of a red blood corpuscule (MCV), platelet count (Plt) and C-reactive protein level (CRP); and average APACHE II results were all attached in Table 1.

Table 1. The mean results of white blood cells count (WBC), the hematocrit (Hct), the average volume of a red blood corpuscule (MCV), platelet count (Plt), C-reactive protein level (CRP) and outcomes in Acute Physiology And Chronic Health Evaluation II (APACHE II) severity-of-disease classification system; between male and female subgroups, divided.

		WBC (*10³/uL)	Hct (%)	MCV (fL)	Plt (*10³/uL)	CRP (mg/l)	APACHE II (points)
Female	mean	10.5	39.4	86.7	268.8	76.1	3.8
n = 289	SD	5.75	4.22	4.24	71.81	105.40	5.04
Male	mean	11.3	41.6	87.7	238.0	81.9	5.1
n = 166	SD	5.22	5.02	4.59	94.17	108.54	5.83
	p	*ns*	<0.001	<0.05	<0.01	*ns*	<0.05

Period from admission to surgical procedure in this subgroup was on average 13.8 (SD 21.64) hours and the mean hospital stay duration was 80.7 (SD 87.21) hours. Laparoscopic cholecystectomy was underwent in 303 (92.9%) patients, open surgery was in 9 (2.7%), laparoscopic converted to open cholecystectomy was in 13 (3.5%) of them, while in 1 (0.2%) case the ultrasound guided cholecystostomy was performed. Causes of conversion were given in Table 2. There was statistically signifilicant difference between female and male patients (p <0.005). Mean duration of the procedure in this subgroup was 77.6 (SD 39.28) minutes. Intraoperatively the results were: cholecystolithiasis without cholecystitis in 155 (47.5%) female patients; calculous cholecystitis in 95 (29.1%); hydropic gallbladder in 27 (8.3%); gallbladder empyema in 27 (8.3%); gangrenous gallbladder in 14 (4.3%); perforated gallbladder in 6 (1.8%); and polyps of gallbladder was in 2 (0.6%) of the cases in this subgroup. The intraoperative outcomes were shown in Table 3. Histopathological results in this subgroup were: malignant tumor in 3 (0.9%) cases; polyp of gallbladder in 1 (0.3%); intact gallbladder in 2 (0.6%); gallstones without

Table 2. Causes of conversion from laparoscopic to open cholecystectomy, between male and female subgroups, divided.

	Cause	**Female** (n = 13)	**Male** (n = 22)
1	Inflammatory infiltration of hepatic hilar area	6	7
2	Difficulties in identification Calot's triangle structures	4	10
3	Common bile duct rupture	2	0
4	Hemorrhage of hepatic artery branches	0	4
5	Abscess of the Calot's triangle	0	1
6	Fistula between gallbladder and duodenum	1	0

Table 3. Intraoperative investigations and histopathological results of removed gallbladders, between male and female subgroups, divided.

	Female	**Male**		**Female**	**Male**
intraoperative	n = 326	n = 178	**histopathological**	n = 326	n = 178
Cholecystolithiasis without cholecystitis	155	48	Intact	2	0
Calculous cholecystitis	95	65	Polyp	1	2
Hydropic	27	5	Adenocarcinoma	3	0
Empyema	27	29	Chronic	186	81
Gangrenous	14	21	Ulcerative	42	10
perforated	6	1	Phlegmonous	60	41
Acalculous necrotic and hemorrhagic cholecystitis	0	7	Gangrenous	26	27
Polyp	2	2	Necrotic	6	17

cholecystitis in 2 (0.6%); changes of gallbladder wall: chronic inflammatory in 186 (57.6%), ulcerative in 42 (12.9%), empyematous in 60 (18.4%), gangrenous in 26 (7.9%), necrotic and hemorrhagic in 6 (1.8%). Histopathological results were listed in Table 3. The average length of the gallbladder during histopathological investigation was 88.5 (SD 2.33) mm. Postoperative complications occurred in 41 (12.6%) cases, wherein 25 were surgical and 16 were non-surgical. 8 females in this subgroup required ICU stay postoperatively (2.5%). The mortality rate was 1.8% (n = 6).

Male subgroup

The amount of male patients in this study was 178 with mean age of 52.4 (SD 16.12) years old, wherein scheduled (n = 73, 41%) and emergency (n = 105, 59%) cases. Average period of time from start of pain to admission was 10.2 (SD 11.40) days. According to past medical history, duration of symptoms was: 0–24 hours in 15.8% of the cases, 2–7 days in 39.5%, 2–4 weeks in 8.8%, 2–12 months in 25.4%, 2 or more years in 7% of them. 3.5% of the cases were asymptomatic. Pain complaints were constant in 36.3% of the cases, or colic in 59.8%. Subjective pain location was: below right costal arch in 83.5%, epigastrium in 8.7%, whole abdomen in 5.2%, other in 2.6%. Pain severity score according to NRS was on average 3.2 (SD 3.03). Physical status results measured with ASA were: ASA I — n = 106, 59.6%; ASA II — n = 37, 20.8%; ASA III — n = 22, 12.4%; ASA IV — n = 13, 7.3%. During examination, abdomen in supine position was: distended in 28.8%, scaphoid in 11.5%, and flat in 59.6%. Sore tenderness on admission was investigated: below right costal arch in 84% of the cases, in epigastrium in 9%, the whole abdomen in 5%, other in 2%. Muscle guarding was in 73.5% of the patients, and Blumberg's sign was in 9% of them. The mean results of the blood test outcomes such as WBC, Hct, MCV, Plt and CRP; and average APACHE II results were all listed in Table 1. Time between admission and surgical procedure in male patients was in mean 18.7 (SD 26.16) hours; the average length of hospital stay was 92.5 (SD 81.46) hours. 147 (82.6%) patients underwent laparoscopic cholecystectomy, while open surgery was in 9 (5.1%). In 22 (12.4%) of them primary laparoscopic procedure was converted to open cholecystectomy. Reasons for conversion were listed in Table 2. Mean duration of the procedure in this subgroup was 95.5 (SD 46.08) minutes. Intraoperative investigations were: cholecystolithiasis without cholecystitis in 48 (27.0%) male patients; calculous cholecystitis in 65 (36.5%); hydropic gallbladder in 5 (2.8%); gallbladder empyema in 21 (11.8%); gangrenous gallbladder in 21 (11.8%); perforated gallbladder in 1 (0.6%); and acalculous necrotic and hemorrhagic cholecystitis in 7 (3.9%) cases. The intraoperative results were shown in Table 3. According to the outcomes listed above, the dissected gallbladders were histopathologically reported as: polyp of gallbladder in 2 (1.1%); intramural gallbladder changes: chronic inflammatory in 81 (45.5%), ulcerative in 10 (5.6%), empyematous in 41 (23%), gangrenous in 27 (15.2%). Histopathological results were listed in Table 3. The average length of the gallbladder during histopathological investigation was 86.5 (SD 1.72) mm. Postoperative complications occurred in 24 (13.5%) of the cases, wherein 13 were nonsurgical and 11 were surgical. 6 males in this subgroup required ICU stay (3.4%). The mortality rate was 2.8% (n = 5).

Discussion

The number of treated females was significantly higher than males in this study (326 vs. 178, p <0.05), which is correct in correlation to epidemiological studies [1–2, 22]. However, while the amount of emergency, acute admission was 1.5 times more often in males than females, the scheduled ones was 1.5 times less frequent in men than women, surprisingly [23]. It is well known that emergency admission comes with higher amount of subsequent eventual intraoperative and postoperative complications [7, 23]. Therefore higher number of scheduled operations in female patients without further discriminating parameters a priori differentiates the results between both subgroups. The average age was higher in men (56.3 vs. 52.7 years old, p <0.05). This value has undoubtedly a strong impact in determining worse prognosis in men. Past medical history was not significantly different between both subgroups. The period of pain complaints (10.2 days in male vs. 12.5 days in female, *n.s.*) and the location of pain were both similar in each subgroup — right upper abdominal quadrant and epigastrium. Nevertheless, the average NRS results were significantly higher in male cases (4.1 vs. 3.2, p <0.02). Perhaps the higher percentage of emergency admissions and hence the acute, strong pain instead of indications of scheduled cholecystectomy, force men to find an adequate medical help. Unfailingly, the subjective pain complaints are the consequence of more advanced inflammatory process in males, as confirmed in histopathological results [15]. The only results significantly different in ASA score were in ASA IV. Critical chi square values for different groups were 0.5 (ASA I), 0.6 (ASA II), 0.05 (ASA IV) and 4.2 (ASA IV) (0.02< p <0.05) respectively. Thus, the higher amount of women than men without life threatening complaints were cured. The shape of abdominal cavity in supine position was distended more often in females, while men had scaphoid abdomen more likely. Due to that fact, the thickness of the abdominal wall was statistically narrower in men, thus the accessibility of the interior organs such as gallbladder should be much easier, whereas in male subgroup both length of surgical procedure and conversion percentage was significantly higher. Some can venture to say that in contrast to literature data, obesity in our group of patients did not affect the length of the procedure or depend on the risk of conversion. Physical examination during admission revealed muscle guarding in 84% men and 72.8% women (*n.s.*), while rebound tenderness in 9.7% vs. 8.9% respectively (*n.s.*). In laboratory tests, mean HCT (41.4 male vs. 39.2 female, p <0.05), mean Plt (242.2 male vs. 269.6 female, p <0.05) and mean MCV (87.7 male vs. 86.7 female, p <0.05) were all significantly different. Furthermore, APACHE II results were also statistically significant (5.1 male vs. 3.7 female, p <0.05). However, it did not affect mortality (chi squared value = 0.4), ICU stay necessity, or complications (both surgical and non-surgical). The majority of the procedures were laparoscopic in both subgroups respectively. Male patients under-

went laparoscopic converted to open cholecystectomy more often (22 vs. 13, p <0.001). Therefore, some can put forward a thesis confirmed in the literature that the number of conversions is definitely higher among men [11, 14, 15]. It is of importance to notice that surgical complications in men were statistically sparser (p <0.01). Paradoxically, it may be connected with conversions to open surgery thus more accessibility to intraoperative manual control of the organs [24, 25]. Male cases in this study had higher percentage of ICU stay necessity (3.4% vs. 2.5%, *n.s.*), mortality (2.8% vs. 1.8%, *n.s.*), mean length of hospital stay (92.5 hours vs. 80.7 hours, *n.s.*), period of time from admission to surgical procedure (18.6 hours vs. 13.8, p <0.05). These confirm the conclusions contained in some publications about the benefits of planned cholecystectomy [7, 14, 23]. Nevertheless, mean duration of the procedure was longer in males than females with very strong statistical significance (95.5 minutes versus 77.6 minutes, p <0.0005). Undoubtedly the amount of conversions has strong impact on it (p <0.01). However, the most frequent reason for conversion was technical difficulties in preparing Calot's triangle structures due to inflammatory process instead of anatomical abnormalities, surprisingly. Advanced inflammatory processes of the gallbladder were investigated intraoperatively more often in men, hence the confirmation of it is the higher percentage of advanced changes in histopathological examination in male. Characteristic for this study was the statistical importance for minimal intraoperative investigations (i.e. cholecystolithiasis without cholecystitis), which was not reflected in the results of histopathological diagnosis of chronic cholecystitis (*n.s.*). However, macroscopic findings such as empyema and gangrenous gallbladder were statistically significant (p <0.05) and confirmed by histopathological outcomes where gangrenous or necrotic gallbladders were diagnosed more often in male cases (p <0.05). Furthermore, the number of ulcerative gallbladders in men was negligible (n = 10, 5.6% vs. n = 42, 12.9%, p <0.05). These data are divergent with opinions about a more severe course of the inflammatory process in men and with the theory about the protective role of estrogen for connective tissue in women [15, 26–30], and are in contradiction to the latest study of Brazilian authors who stated that gender is not a factor risk in laparoscopic cholecystectomy outcomes [31]. In conclusion, statistical difference occurred in parameters such as age, type of admission (emergency/scheduled), NRS results, ASA score, APACHE II results. This proves that in order to obtain more reliable results, the criteria for selection of patients for particular subgroups should be more uniform and narrow, because the heterogeneity of the groups determines the difference in the received parameters of surgical procedure such as length of surgery, type of surgery, percentage of conversion, postoperative complications. Such a heterogeneous patient selection and therefore ambiguous obtained results can actually give the impression that gender is a factor differentiating cholecystectomy results.

Conclusions

- Differences between genders in the course of surgical treatment of cholecystolithiasis are due to both somatic and also behavioral conditions, e.g. type of admission, greater sensitivity to pain and longer period of time since the onset of symptoms to the hospital admission.
- On the basis of this study, statistically significant differences between both genders were found, but this may be due to a significantly larger number of men undergoing emergency procedures.
- It cannot be unequivocally determined that male gender is an independent risk factor for cholecystectomy, notwithstanding the foregoing findings for significant differences in the investigated parameters.
- Further research studies should be carried out taking into account more sophisticated parameters with the patient's gender.

Conflict of interest

None declared.

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