Daniel Francisco Muñoz Nogales
Final Master’s Thesis

ACUTE CHOLECYSTITIS: CAUSES OF DEATH.
TEN YEARS META ANALYSIS.

Principal supervisor: dr. Juozas Juočas
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SUMMARY

Author of master thesis: Daniel Francisco Muñoz Nogales.


Aim of research: To determine the principal causes of death in Acute Cholecystitis of last ten years according to the patient’s characteristics, type of disease, comorbidities and risk factors, pathophysiology, histopathological changes and management of disease.

Objectives of research: 1. Determine the principal causes of death in Acute Cholecystitis of last ten years evaluating and comparing deceased patients from acute cholecystitis according to cholecystitis type and patient’s characteristics. 2. To compare mortality rate of acute cholecystitis management according the type, timing and possible complications of surgery (early or delayed). 3. Evaluate and compare the mortality rate by years, distributing the patients in two groups: first group from 2008 to 2013 and second group from 2014 to 2018.

Methods: Object of master thesis research were systematic search of articles and guidelines from last ten years: PubMed, Medline, Embase, the Cochrane Library and Web of Science. Retrospective research and clinical data of all deceased patients for Acute Cholecystitis from 2008 to 2018 was performed at the department of General Surgery (Kauno Klinikinė Ligoninė, Kaunas, Lithuania). The distribution of patients is based on clinical data regarding deceased patient’s age, gender, time of onset, hospitalization period, pathophysiology, histopathological changes, type of surgery, risk factors to develop complications and time of death (groups by years) were collected. Statistical analysis was performed by applying “Excel for Mac 2018” (Cupertino, California, USA) and “SPSS statistics” (IBM Corporation, Armonk, New York, USA).

Results: Mortality rate in the last ten years in the department is 1.47%. The risk factors in reviewed deceased patients, individually analyzed, were 67.7% of elderly, 61.3% were critically ill patients and 19.4% with concomitant Diabetes Mellitus. The median age was 84 ± 11 years old. In our study the male-female ratio was 41.9% males and 58.1% females. In the study the most common causes of death in acute cholecystitis are: Multiple Organ Dysfunction Syndrome with 54.8% and Sepsis with 45.2%. The 57.9% of critically ill patients had an ASA IV and 42.1% had ASA III (p=0.04).

Conclusions: 1. Women who are more than 75 years old has the highest mortality rate. 2. Mortality rate is significantly higher in elderly patients (>75 years old). 3. Most common causes of death in acute cholecystitis are: Multiple Organ Dysfunction Syndrome (54.8%) and Sepsis (45.2%). 4. The 96.7% of deceased patients have ASA III or ASA IV. 5. The most common histopathological changes of acute cholecystitis related to death are: gangrenous gallbladder (38.7%), gallbladder perforation (29%), phlegmonous gallbladder (32.3%). 6. Laparoscopic cholecystectomy is the treatment of choice.
ACKNOWLEDGEMENTS

This research is a part of my integrated studies in the Lithuanian University of Health Sciences as a Final Master Thesis, during my 6th year of medical studies.

I would like to thank personally prof. dr. Juozas Juočas who helped, taught and advised me throughout the whole research work.
CONFLICT OF INTEREST

The author reports no conflicts of interest.

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Research of master thesis is approved by ethics committee (no. of permission BEC-MF-121)
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<th>Abbreviation</th>
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<td>AAC</td>
<td>Acute acalculous cholecystitis</td>
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<td>ACC</td>
<td>Acute calculous cholecystitis</td>
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<td>ASA</td>
<td>American Society of Anesthesiologists score</td>
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<td>BDI</td>
<td>Bile duct injuries</td>
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<td>BMI</td>
<td>Body mass index</td>
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<td>ESWL</td>
<td>Extracorporeal shockwave lithotripsy</td>
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<td>INR</td>
<td>International normalized ratio</td>
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<tr>
<td>MODS</td>
<td>Multiple organ dysfunction syndrome</td>
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<td>MOF</td>
<td>Multiple organ failure</td>
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<td>PC</td>
<td>Percutaneous cholecystostomy</td>
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<td>PT</td>
<td>Prothrombin time</td>
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<td>RCTs</td>
<td>Randomized controlled trials</td>
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<td>SD</td>
<td>Standard Deviation</td>
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<td>SOFA</td>
<td>Sequential Organ Failure Assessment</td>
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INTRODUCTION

The most frequent gallbladder disease is cholelithiasis (95%) [1,2], of all patients admitted for gallbladder disease, 20% of them have acute cholecystitis [2]. Acute calculous cholecystitis (ACC) is three times more frequent in women than in men and up to 50 years old [2].

Main causes of death of acute cholecystitis are related to life-threatening complications of the disease, including gallbladder gangrene and gallbladder perforation [2] that may lead to peritonitis, sepsis and finally death [3,4]. Another important cause of death are the surgical complications, usually seen in elderly and critically ill patients [5].

Nowadays the quality of life increased, the elderly population gradually become bigger and the prevalence of acute cholecystitis also increases. The most important factor increasing the post-operative mortality and morbidity is age, [6,7] many comparative analyses shows that elderly group (> 75 years old) has a significant difference according morbidity and mortality than patients under those age [8].

Many randomized controlled trials (RCTs) shows that the early laparoscopic cholecystectomy is associated with a shorter hospitalization period, less morbidity and mortality but other studies shows an association between early surgical management and increase of morbidity and mortality [9].

In light of this, I performed a meta-analysis of articles and guidelines and retrospective research of deceased patients of past ten years in the Department of Surgery of Kaunas Clinical Hospital (Kauno klinikinė ligoninė, Kaunas, Lithuania), to evaluate and compare deceased patients from acute cholecystitis according disease and patient’s characteristics, establish the relation between acute cholecystitis complications, age, comorbidities and risk factors with patient’s mortality and compare mortality rate of acute cholecystitis according the type of cholecystitis, complications and timing of surgery (early or delayed).
AIM AND OBJECTIVES OF RESEARCH

Aim: To determine the principal causes of death in Acute Cholecystitis of last ten years according to the patient’s characteristics, type of disease, comorbidities and risk factors to develop complications, pathophysiology, histopathological changes and management of disease. Evaluate and compare the mortality rate by years.

Objectives:

1. Determine the principal causes of death in Acute Cholecystitis of last ten years evaluating and comparing deceased patients from acute cholecystitis according to cholecystitis type and patient’s characteristics (age, gender, time of onset, hospitalization period, pathophysiology, histopathological changes, type of surgery and risk factors to develop complications).

2. To compare mortality rate of acute cholecystitis management according the type, timing and possible complications of surgery (early or delayed).

3. Evaluate and compare the mortality rate by years, distributing the patients in two groups: first group from 2008 to 2013 and second group from 2014 to 2018.

4. To establish the relation between acute cholecystitis complications, age, comorbidities and risk factors to develop complications with patient’s mortality.
1. LITERATURE REVIEW

1.1 Acute cholecystitis and causes of death.

Acute cholecystitis is an onset of inflammation of the gallbladder, most often caused by gallstones [10].

1.1.1 Main causes of death in acute cholecystitis.

Main causes of death of acute cholecystitis are related to life-threatening complications of the disease, including gallbladder gangrene and gallbladder perforation [11] that may lead to peritonitis, sepsis and finally death [3, 4]. Another important cause of death are the surgical complications, usually seen in elderly and critically ill patients [5].

The obstruction of the cystic duct causes an inflammatory process that develops in acute cholecystitis, followed by distension and subsequent chemical or bacterial inflammation of the gallbladder. Severe form of disease may lead to necrosis of the gallbladder wall, known as gangrenous cholecystitis. The inflammatory process produces macroscopic and microscopic changes in the gallbladder. People with acute cholecystitis usually have unremitting right upper quadrant pain, fever, anorexia, nausea and vomiting [10].

1.1.2 Direct causes of death in acute cholecystitis

The death causes of acute cholecystitis can be related with:

- Multiple organ dysfunction; associated with severe disease (Grade III). The multiple organ dysfunction syndrome (MODS) or multiple organ failure (MOF) can lead to death without emergency treatment [12]. One or more of this failure can be seen:
  - Respiratory dysfunction, decreasing the PaO₂/FiO₂ ratio in less than 300 mmHg, may lead to acute respiratory failure and finally death [12].
  - Hepatic failure, when prothrombin time (PT) or international normalized ratio (INR) is more than 1.5.
  - Neurological dysfunction, decreasing the consciousness and responsiveness.
  - Cardiovascular dysfunction, the blood pressure decreased to hypotension.
  - Renal dysfunction, serum creatinine levels increase more than 2 mg/dl, and oliguria is present.
  - Hematological dysfunction, platelet count decreases to less than 100.000 mm$^3$ [12].
• Sepsis; preceded by gallbladder gangrene and perforation [11]. Perforation may lead to peritonitis, sepsis and finally death [3,4].

• Surgical complications; an important cause of death are the surgical complications, usually seen in elderly and critically ill patients [5]. The mortality due to surgical complications is usually related to underlying comorbidities of the patient as well as sepsis [13]. However, laparoscopic cholecystectomy in acute cholecystitis has the lowest mortality rate according to other gastroenterological surgeries, about 5.6-7.2% [14].

1.2 General rates of morbidity and mortality in acute cholecystitis.

Acute cholecystitis is caused mainly by gallstones in about 90-95% of patients, acute calculus cholecystitis (ACC) and the other 5-10% without gallstones, acute acalculous cholecystitis (AAC) [2].

The morbidity and mortality rates between ACC and AAC are different and depends on several factors.

AAC is a pathology that is diagnosed with increasing frequency in critical patient due to major trauma, such as extensive burns, multiple traumas, severe infection, in some cases of chemotherapy though hepatic artery, in patient with prolonged parenteral nutrition, end stage renal disease and other clinical conditions [15,16]. AAC is a life-threatening condition and has higher rates of morbidity and mortality than ACC [17]. AAC is usually seen in critically ill patients and in post-operative biliary tract surgery patients, with a mortality rate of 41% and morbidity rate of 82% [18].

AAC has higher incidence in male patients up to 50 years old. About 80% of patients who develop AAC following surgery without trauma are men [19]. This is an emergency and life-threatening condition that has high incidence to develops to gangrene, perforation and finally death without an instant treatment. Early management drops the mortality rate 7% of 65% in delayed management [20].

Riché et al, reported a significant difference in mortality rate in patients with septic shock (35%) and without it (8%) [21].

The most frequent isolated microorganisms that we can found in patients diagnosed with AAC are Escherichia coli and other gram-negative enteric bacteria, we can also find many of other agents
related with this pathology like *Salmonella ssp*, *Plasmodium falciparium*, *Cryptosporodium*, cytomegalovirus, varicella zoster, hepatitis A virus, Epstein-Barr virus and *Candida* spp. [22,16]. The septicemia may occur as complication of major surgery and usually develops in gangrenous cholecystitis with high mortality rate [3]. *McChesney et al*, reported 46% of mortality rate in this group of patients [3].

1.2.1 Epidemiology and Incidence according mortality.

The acute cholecystitis has higher incidence in women than in man up to 50 years of age, is about 1,5 times more common in women [10]. The main risk factor to develop gallstone disease are age, gender, BMI, hemolytic diseases, pregnancy, diabetes mellitus and hepatic diseases [23]. AAC is seen more commonly in critically ill patients or after trauma, also in elderly patients, post-operative, diabetes mellitus, metastatic tumors, vasculitis and heart diseases. AAC has higher mortality rate than ACC [24]. The mortality rate is high due the difficulty of diagnosis in the group of critically ill and injured patients, remaining about 30%. The complication development in AAC is also high, the gangrenous cholecystitis incidence is about 50% and 10% of perforation incidence, which are life-threatening conditions [24].

According to the Multicenter Italian Study on Cholelithiasis (MICOL), the incidence of gallstone disease was 18.8% in women and 9,5% in men, after examination of approximately 33,000 subjects with aged between 30 to 69 years old in 18 cohorts of 10 Italian regions [10].

The incidence of acute cholecystitis is about 20% among people with biliary colic, with wide variation in severity. Biliary colic occurs in 1% to 4% of people with gallstones.

About 10-15% of the population of developed countries suffers from gallstones. Of people admitted to hospital for biliary tract disease, 20% have acute cholecystitis [25].

1.3 Differences in mortality and morbidity

1.3.1 Differences according age.

The age is an important risk factor that increases or decreases the mortality and morbidity rate. Patients older than 75 years old have an increased mortality and morbidity rates. Elderly patient has increased risk for developing gangrenous cholecystitis [8].
Ekici et al, reported that there is a significant difference in: the rate of surgery due to ACC, postsurgical complications and morbidity, conversion to an open surgery and hospitalization period, that were statistically higher in patients in the age group older than 60 years old [1].

Kirshtein et al, shows that the patients older than 75 years old have a mortality rate of 4.8% and morbidity rate of 31%, comparing with those patients under 75 years old that have 0.5% of mortality rate and 15% of morbidity rate, it was a significant difference between the two groups [27].

Nielsen et al, shows that there is a significant difference in patients with ACC that are in the age group of more than 80 years old, with an odd ratio for mortality of 30.9% comparing with those in the age group of 65-79 years old with 5.5% and 50-54 years old with 1% [28].

1.3.2 Differences according septic shock.

The difference in mortality between patients with septic shock or without it is very significant [29]. The septic shock may appear after a generalized peritonitis due to gallbladder complications as perforation or gangrene [18]. Patients who develops septic shock has about 35% of mortality rate and patients without septic shock has 8% [29]. Septic shock or severe sepsis can also appear after surgery, it increases strongly the mortality rate till 43% [4].

1.3.3 Differences according phlegmonous acute cholecystitis and gangrenous acute cholecystitis.

Have been reported differences between phlegmonous and gangrenous cholecystitis according to conversion surgery and subsequently mortality and morbidity rate [5]. Ciftci et al reported a rate of conversion to open surgery of 43.7% in gangrenous cholecystitis and 28.1% in phlegmonous cholecystitis patients [30].

1.4 Management according Morbidity and Mortality.

When we are talking about ACC the main point is to try to treat it in a conservative way. The conservative management is the first line treatment, and the goal is that the gallstones that are obstructing the cystic duct can lead to the disimpaction and the falling back into the gallbladder, permitting the emptying of the duct. If the first line of treatment is not successful and the gallstone persist obstructing the cystic duct, the complications and perforation may result, and urgent measures must be taken [10]. Perforation usually lead to peritonitis and sepsis, and it is associated with a high morbidity and mortality rates [4].
Generally, a patient suffering acute cholecystitis is hospitalized, monitored, hydrated and electrolytes are restored intravenously [31]. Oxygen therapy and analgesia is given. Analgesics shouldn’t be derived from morphine to prevent the spasm of Oddi sphincter.

The antibiotic therapy should be initiated empirically due to the risk of infection, usually if the patient is not improving after 12-24 hours or has systemic signs. The antibiotic treatment should be prescribed for gram negative and anaerobic bacteria due to suspicion of involvement of *Escherichia coli* [31,10]. The broad spectrum antibiotic therapy is an important factor that affects mortality rates after surgery, specially in critically ill patients. Empiric treatment with broad spectrum antibiotic therapy is always necessary to prevent complications and decrease the mortality rate after surgery [32]. In AAC fungi and anaerobes bacteria are usually found in bile culture of diabetic patients and elderly people. Antibiotic therapy in AAC is not substitute for sanitation of necrotic focus but remains an important associated therapy [33].

Non-surgical treatment consists on gallstone dissolution therapy, treatment of selected patients with cholesterol gallstones [34], or extracorporeal shockwave lithotripsy (ESWL), treatment that have been used for chronic patients with calculous cholecystitis unable to perform surgery, but not in acute cholecystitis patients [10].

Surgery is the definitive treatment of acute cholecystitis. Next to 20 % of patients diagnosed with acute cholecystitis need emergency surgery [10], it is indicated in the first 72 hours of the onset of the disease [31]. Early surgery for acute cholecystitis decreases the possibility of complications and has lower conversion rate in comparison to delayed surgery [10].

Video guided laparoscopic cholecystectomy is the best treatment in AAC and ACC. The main point of laparoscopic cholecystectomy is based on reduced the magnitude of the surgical trauma, leading to diminish the inflammatory, metabolic and immunological reaction, compared to laparotomy [31]. Early cholecystectomy may lead to the higher possibility of complications and mortality in high risk patients [35].

There is a significantly difference in mortality and morbidity rates between early and delayed cholecystectomy. Early or immediate surgery is performed in the first 72 hours of the onset of disease. Morbidity rate is much higher in delayed laparoscopic cholecystectomy, in about 35%, than in the early cholecystectomy, that is about 12%. [39].
Early cholecystectomy is considered the best treatment in patient with acute cholecystitis and should be the treatment of choice for operable patients [35]. Elderly and critically ill patients are in high risk of conversion from video guided laparoscopic cholecystectomy to an open cholecystectomy surgery [5]. The main risk factors for conversion are male gender, obesity, hepatic cirrhosis, adhesion due to previous surgery procedure and old age. The combination of these factors and other concomitant diseases increases heavily the risk of conversion [32]. They have more than 40% of probabilities to develop any complication during surgery and about 4% of mortality [5].

P. Ignatius et al, reported that, after a retrospective study in the Hospital of Lithuanian University of Health Sciences, the treatment of choice for acute cholecystitis is laparoscopic cholecystectomy. Optional treatment for critically ill patients is percutaneous cholecystostomy (PC), obtaining a statistically significant difference decreasing the WBC’s count and C-reactive protein level after the procedure. PC may be used as temporizing measure or as a definitive treatment for acute cholecystitis in critically ill patients [40].

Barauskas G. et al, reported after the prospective study of bile duct injuries (BDIs) incidence after laparoscopic cholecystectomy at the Clinic of Surgery of Lithuanian University of Health Science from 2000 to 2007, that the incidence of BDI in acute cholecystitis after the surgery was 0,62%. The overall incidence was 0,24% and major injuries of bile duct after laparoscopic cholecystectomy was 0,11%. BDI is a life-threatening condition that may lead to death without an appropriate and early treatment, associated morbidity and prolonged hospitalization period increases three times the risk of death [41]. The BDI management should be performed in tertiary specialist centers to improve the outcomes [42].

The mortality rate after cholecystectomy is about 13-23%. The most common cause of death after surgery is the multiple organ failure, usually most of these patients died later than the first week after surgery [36]. Septic shock or severe sepsis are severe complications that can also appears after surgery, it increases strongly the mortality rate till 43% [4].

Based on the study of Jouko Laurila about “Surgically treated acute acalculous cholecystitis in critically ill patients” with the assent of the Faculty of Medicine, University of Oulu, Oulu University Hospital, on May 26th, 2006, in the mortality rate after surgery there is not statistically difference in age, gender, body mass index (BMI), duration of ICU period, SAPSII or SOFA scores between living and deceased patients after surgery [36].
1.4.1 Differences according ASA score in morbidity rate.

Yi et al, reported a significant difference in the morbidity rate and surgical risk factors according American Society of Anesthesiologists score (ASA). ASA I with 9.1% of morbidity rate and ASA III with 20% [37].

1.4.2 Modern tactics in surgical treatment of acute cholecystitis

PC is a minimally invasive procedure under local anesthesia, and the procedure of choice of severe comorbidity or high-risk patients [38,40].

Allow the gallbladder decompression and swelling management. Is usually used in critically ill patients as a temporary procedure until the symptoms allows the surgeon to perform a cholecystectomy, about 6 or 8 weeks after the remission of acute cholecystitis. The mortality rate of this procedure is low, about 3% of patients die after the procedure [16].

Endo et al, reported that in patients with Grade III of severity of acute cholecystitis, it is safe to perform cholecystectomy with previous PC. PC has a beneficial role in high risk patient groups with comorbidities or severe disease [43].

1.4.3 Mortality rate associated to elderly patients in perioperative period.

The old age is an important risk factor in acute cholecystitis patients, we are talking about elderly patients when the age is more than 80 years old [32]. Lupinacci el al, shows that elderly patients’ group with acute cholecystitis, the mortality rate increases dramatically till 34% in early cholecystectomy, also they need ICU more commonly, have higher possibilities to develop a complication and the hospitalization period is much longer [44].

1.4.4 Mortality rate associated to concomitant diabetes mellitus in perioperative period.

Diabetes mellitus as a concomitant disease in acute cholecystitis should be considered a risk factor for the development of complications, due to the relation of the disease with cardiovascular diseases and bacterial spreading after the cholecystectomy surgery [32]. According recent studies, the mortality rate for patients with diabetes mellitus is increased 4.4% [45]. Early cholecystectomy in the first 24h of the onset of symptoms has better prognosis and decreases the risk of post-surgical complications and hospitalization period length [46].
The cardiovascular events and acute renal failure risk after cholecystectomy surgery are higher in patients with concomitant diabetes mellitus with insulin non-oral treatment, as well as the risk of develop a surgical infection, sepsis or preoperative perforation [45].

1.5 Complications according mortality

The main complications of acute cholecystitis are: gangrene and perforation of the gallbladder, pericholecystic abscess and cholecystoduodenal fistula [47].

1.5.1 Gallbladder perforation.

Perforation of the gallbladder is a serious complication and live threatening condition. The mortality rate of gallbladder perforation is very high and most of the cases are diagnosed during the surgery [48].

The gallbladder inflammation may develop into ischemia and then necrosis, resulting in a gallbladder perforation in approximately 2-11% of patients diagnosed with ACC [48]. Patients are usually elderly, female and with serious comorbidities [49]. The perforation may occur also in patients with AAC without surgical emergency treatment, due to the rapid progression of the complication [50]. About 15% of patients with AAC develops a perforation complication, consequently it increases the mortality rate [51].

Gallbladder perforations are divided into three types since Niemeier classified them in 1934 [33]: type I gallbladder perforation, is associated with biliary peritonitis (16%), it has the highest rate of mortality, type II gallbladder perforation, is related with abscess formation (68%) and type III gallbladder perforation, that is related with fistula formation with adjacent structures (16%) [49].

1.5.2 Gangrenous cholecystitis.

Between 2 and 30% of patient admitted for acute cholecystitis develop gangrenous cholecystitis as a complication of the disease. Male patients with acute cholecystitis, older than 50 years old, cardiovascular disease history and leukocytosis greater than 17.000 cells/mL have the highest risk of gallbladder gangrene. Urgent laparoscopic cholecystectomy needs to be considered for the patients at high risk of the gallbladder gangrene and a low threshold to change to laparotomy cholecystectomy procedure [52].

AAC is closely related to gangrenous gallbladder, 63% of AAC patients develops gangrene as a complication of the disease with high incidence of death [18].
Mortality rate of complicated acute cholecystitis with gallbladder gangrene has been reported in many studies and they conclude that is approximately 40-50%, very high compared with uncomplicated acute cholecystitis [51,53].

1.5.3 Pericholecystic abscess.

The abscess formation is not a common complication, but it can be diagnosed easier due to better imaging recognition. Pericholecystic abscess can be classified into three types according to ultrasonography findings of localization of abscess, type I with the abscess location adjacent to gallbladder, can be treated conservatively as well as type II, with intramural abscess location and type III with intra-peritoneal location of the abscess and this type requires emergency surgery [49].

1.5.4 Cholecystoduodenal fistula.

The cholecystoduodenal fistula is a rare complication of cholelithiasis [54]. The cholecystoduodenal fistula is the most common type (70%) of fistula formation as a complication of acute cholecystitis [49]. The symptoms of cholecystoduodenal fistula are not specific and the diagnosis is not easy. Must be considered as complication in elderly patients with contracted gallbladder and adhesions [54].
2. RESEARCH METHODOLOGY AND METHODS

Research planning (organization):

The planning of the research is composed of, firstly, systematic search of articles and guidelines from last ten years, the collection and analysis of theoretical data and literature of the disease of the last ten years, creating design of investigation and collecting permissions and data. Finally, statistical analysis of deceased patient with the main diagnosis of acute cholecystitis in the department of General Surgery (Kauno Klinikinė Ligoninė) of last ten years (from 2008 to 2018), results, conclusions and preparation of presentation.

The object of study:

Determine and analyze the principal causes of death in Acute Cholecystitis of last ten years, from 2008 to 2018, according to the patient’s characteristics, type of disease, comorbidities and risk factors to develop complications, pathophysiology, histopathological changes and management of disease. Evaluate and compare the mortality rate by years, distributing the patients in two groups: first group from 2008 to 2013 and second group from 2014 to 2018. To compare mortality rate of acute cholecystitis management according the type, timing and possible complications of surgery (early or delayed).

Participant selection (population sample):

Deceased patients with the main diagnosis and cause of death of acute cholecystitis of past ten years (2008-2018) that have been hospitalized and treated in the department of Surgery of Kaunas Clinical Hospital (Kaunas, Lithuania). Thirty-one deceased patients were selected for the research.

Research methods:

This research was retrospective and descriptive. First was necessary a literature review and systematic search of articles and guidelines from last ten years: PubMed, Medline, Embase, the Cochrane Library and Web of Science. Then the review of clinical histories of thirty-one deceased patients of last ten years (2008-2018) with the main diagnosis and cause of death of acute cholecystitis, obtaining their data like age, gender, risk factors to develop complications, type of cholecystitis, management and direct cause of death. Evaluate and compare the mortality rate by years, distributing the patients in two groups: first group from 2008 to 2013 and second group from 2014 to 2018.
Methods of data analysis:

The analysis was performed using “SPSS” and “Excel for Mac 2018” to calculate the total amount of deceased patients, mortality rates, gender, age of patients, risk factors, hospitalization period, pathophysiology, ASA classification, histopathological changes, type of management and surgery and direct cause of death. The chi-square and independent T-test was used to examine the association between the different variables. Selected values are presented as mean ± standard deviation (SD). For variables, the level of statistical significance (p) was selected.
3. RESULTS

The aim of the study is to make an analysis of main causes of death of acute cholecystitis in the last 10 years, direct causes of death and general rates of mortality by year.

A scientific research, which is aimed to determine the most common causes of death from acute cholecystitis in deceased patients according to the patient’s characteristics (age and gender), comorbidities and risk factors, pathophysiology and histopathological changes. Research participants are deceased population of last ten years (2008-2018) with the main diagnosis and cause of death of acute cholecystitis.

In the Department of General Surgery of Kaunas Clinical Hospital (Kauno klinikinė ligoninė, Kaunas, Lithuania) were analyzed the clinical history of 414 deceased patients in the last 10 years (2008-2018), 31 of them (7,48%) were diagnosed with the main diagnosis of acute cholecystitis and the direct cause of death was related with their principal disease. After study and analysis of those patients, it’s obtained the next data:

- The total amount of hospitalizations with the main diagnosis of acute cholecystitis in 10 years in the department were 2097 patients. The total amount of deceased patients with the main diagnosis of acute cholecystitis were 31 patients (1,47%).

- Mortality rate of acute cholecystitis according to year and total diagnosis of acute cholecystitis in the department: in 2008 the mortality rate was 1,38%, in 2009 was 4,09%, in 2010 was 0,74%, in 2011 was 0,93%, in 2012 0,87%, in 2013 was 0,55%, in 2014 was 2%, in 2015 was 2,27%, in 2016 was 1,61%, in 2017 there weren’t any death reported and in 2018 was 3,04% (Fig. 1).
Fig. 1. Total deaths in acute cholecystitis according total number of patients with the main diagnosis of acute cholecystitis by year.

- Mortality rate of acute cholecystitis in the last ten years (2008-2018) in the department of General Surgery of Kauno klinikinė ligoninė is 1,47%.

From total number of deceased patients of the department in 10 years (414 patients), only the 7,48% were caused by acute cholecystitis (31 patients).

- The hospitalization period median was 8 days (range 5-15).

- The frequency of time of onset in the study was a 35,5% of less than one day (11 patients), 58,1% from one till 3 days (18 patients) and 6,5% for more than 3 days (2 patients).

- Ratio male-female were 41.9% (men) and 58.1% (women) (Fig. 2).

- The median age was 84 ± 11 years old (range 74-90 years).
Analyzing by range of age, 10 of deceased patients were in the range of age of 50-75 years old (32.3%) and 21 deceased patients were in the range of age of >75 years old (67.7%). None of them were under those ranges (<50 years old).

- Physiopathological changes of all deceased patients were divided into: Acute calculous cholecystitis (ACC) with 87.1% (27 patients) and Acute acalculous cholecystitis (AAC) with 12.9% (4 patients) (Fig. 3).
According ASA classification before surgery, 41.9% (13 patients) were classified as ASA IV, 54.8% (17 patients) as ASA III, only 3.2% (1 patient) as ASA II and none of them as ASA I (Fig. 4).

![Fig. 4. ASA classification of patients before surgery of all analyzed patients.](image)

The histopathological changes of acute cholecystitis in our study were composed of: gangrenous gallbladder (38.7%), gallbladder perforation (29%), phlegmonous gallbladder (32.3%) (Table 1).

<table>
<thead>
<tr>
<th>Histopathological changes</th>
<th>Percentage (%)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gangrenous gallbladder</td>
<td>38.7%</td>
<td>12</td>
</tr>
<tr>
<td>Gallbladder perforation</td>
<td>29%</td>
<td>9</td>
</tr>
<tr>
<td>Phlegmonous gallbladder</td>
<td>32.3%</td>
<td>10</td>
</tr>
</tbody>
</table>

The pericholecystic abscess complication have been seen in 3 patients (9.7%), all of them with the histopathological change of gangrenous gallbladder.

All of deceased patients in the study had undergone surgical management.

There were three types of surgery: 10 patients managed by laparoscopic cholecystectomy (32.3%), 19 patients managed by open cholecystectomy (61.3%) and 2 patients managed by percutaneous cholecystostomy (6.5%).

Only one patient had conversion surgery in the study (3.2%).
Timing of surgery divides on Early (<72h) and Delayed (>72h). In the study there were an incidence of 54.8% of early Surgery management (17 patients) and 45.2% of delayed surgery management (14 patients) (Fig. 5).

Analyzing by death time, the time has been divided into: death during preoperative period (not any death reported in this period), death during surgery (3.2%), death during early post-operative period (83.9%) and death during late post-operative period (12.9%).
The risk factors were analyzed individually, any deceased patient can have one, two or all of them. Most common risk factors for the development of complications of all reviewed deceased patients, from more common to less common are: 67,7% of Elderly (21 patients), 61,3% of Critically ill condition (19 patients) and 19,4% with concomitant Diabetes Mellitus (6 patients) (Table 2).

Table 2. Most common risk factors group of reviewed deceased patients.

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Percentage (%)</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critically ill</td>
<td>61,3%</td>
<td>19</td>
</tr>
<tr>
<td>Elderly (&gt;75 years old)</td>
<td>67,7%</td>
<td>21</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>19,4%</td>
<td>6</td>
</tr>
</tbody>
</table>

The 38,7% of deceased patients (12 patients) had both risk factors, elderly and critically ill condition. The three risk factors have been seen in 2 patients (6’45%).

There is a statistical significance between the risk group of critically ill patient condition and ASA classification, the 57,9% of critically ill patients (11 patients) had an ASA IV and 42,1% had ASA III (8 patients) ($p=0,04$).

Most common causes of death in acute cholecystitis in the study were: 17 patients deceased by Multiple Organ Dysfunction Syndrome (MODS or MOF) (54,8%), 14 patients by Sepsis (45,2%) and not any death caused by Surgical complications (Fig.7).

Fig. 7. Most common causes of death in acute cholecystitis of all analyzed patients.
According the date of death and with the purpose of obtain any substantial difference in the acute cholecystitis causes of death by time and to evaluate if there are any statistically difference according the mortality rate of deceased patients, they have been analyzed in two different groups, first group from 2008 to 2013 and second group from 2014 to 2018. After analyze of mortality rate, age, management, hospitalization period and cause of death of acute cholecystitis in both groups, it’s obtained the next data:

**Differences according mortality rate between groups:**

- The mortality rate of first group (2008-2013) was 1,27% of all total diagnosis of acute cholecystitis of 1094 patients.
- The mortality rate of first group (2014-2018) was 1,69% of all total diagnosis of acute cholecystitis of 1003 patients.

**Differences according age between groups:**

- First group (2008-2013) mean of age was 79,3 (± 12) years old with a \( p \) value of 0,319. The median age was 85,5 years old (range 68,2-90 years).
- Second group (2014-2018) mean of age was 82,2 (± 10,6) years old with a \( p \) value of 0,319 (Table 3). The median age was 84 years old (range 74,5-90,5 years).

**Differences according gender between groups:**

- From 14 deceased patients of first group (2008-2013) male mean was 35,7% and female mean was 64,2%. \( p \) value of 0,52.
- From 17 deceased patients of second group (2014-2018) male mean was 47% and female mean was 52,9%. \( p \) value of 0,52 (Table 3).

**Differences according hospitalization period between groups:**

- First group (2008-2013) mean of hospitalization period was 11,5 days and the second group (2014-2018) mean of hospitalization period was 9,35 days with a \( p \) value of 0,03 (Table 3).

**Differences according cause of death between groups:**

- From the total of 14 deceased patients of first group (2008-2013), 8 of them were deceased due to MODS (57,1%), 6 of them the cause was Sepsis (42,9%).
- From the total of 17 deceased patients of first group (2014-2018), 9 of them were deceased due to MODS (52,9%), 8 of them the cause was Sepsis (47%) (Table 3).
### Table 3. Differences between two groups of years of all analyzed patients.

<table>
<thead>
<tr>
<th></th>
<th>2008-2013 (n=14)</th>
<th>2014-2018 (n=17)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality rate</td>
<td>1,27%</td>
<td>1,69%</td>
<td>-</td>
</tr>
<tr>
<td>Age (years)</td>
<td>79,3 (± 12)</td>
<td>82,2 (± 10,6)</td>
<td>0,31</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35,7%</td>
<td>47%</td>
<td>0,52</td>
</tr>
<tr>
<td>Female</td>
<td>64,2%</td>
<td>52,9%</td>
<td></td>
</tr>
<tr>
<td>Hospitalization period (days)</td>
<td>11,5</td>
<td>9,35</td>
<td>0,03</td>
</tr>
<tr>
<td>Cause of death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MODS</td>
<td>57,1%</td>
<td>52,9%</td>
<td>0,8</td>
</tr>
<tr>
<td>Sepsis</td>
<td>42,9%</td>
<td>47%</td>
<td></td>
</tr>
</tbody>
</table>
4. DISCUSSION OF THE RESULTS

In the study we analyzed thirty-one deceased patients of a total amount of 414 deaths from 2008 till 2018. After analysis we obtained all the results that can be compared with the guidelines about the disease and other independent studies in order to determine overall trends.

Mortality rate of acute cholecystitis in the last ten years (2008-2018) in the department of Surgery of Kaunas Clinical Hospital is 1.47%. Of all of deceased patients hospitalized in the department of last 10 years, 7.48% of deaths were related by acute cholecystitis. With the purpose of obtain any substantial difference by time of death and to evaluate if there are any statistically difference according the mortality rate of deceased patients, they have been analyzed in two different groups, first group from 2008 to 2013 and second group from 2014 to 2018, to determine overall trends. In the first group (2008-2013) the mortality rate was 1.27% and in the second group the mortality rate was slightly higher, 1.69%.

In our study we obtain that, analyzing by range of age, 67.7% of the total death from acute cholecystitis were in the range of age of >75 years old, 32.3% of deceased patients were in the range of age of 50-75 years old and none of them were under those ranges. That shows that in our study the mortality rate was significantly higher in the elderly group of >75 years old. The median age was 84 years old (range 74-90 years). According literature; Kirshtein et al, shows that the patients older than 75 years old have a mortality rate of 4.8% and morbidity rate of 31%, comparing with those patients under 75 years old that have 0.5% of mortality rate and 15% of morbidity rate, it was a significant difference between the two groups [27]. Lupinacci et al, shows that elderly patients’ group with acute cholecystitis, the mortality rate increases dramatically till 34% in early cholecystectomy [41].

In our study the male-female ratio was 41.9% males and 58.1% females. According literature, Fialkowski et al reported that ACC is three times more frequent in women than in men and up to 50 years old [2]. In the study we didn’t found any statistically significant difference between physiopathological changes and gender (p=0.4).

Analyzing by physiopathological changes of all deceased patients, the 87.1% had ACC and 12.9% had AAC. According literature, Savoca et al reported that AAC is a life-threatening condition and has higher rates of morbidity and mortality than ACC [17]. Barie et al reported that AAC has higher incidence in male patients up to 50 years old [19].
The risk factors were analyzed individually, any deceased patient can have one, two or all of them. The frequency of risk factors to develop complications in all reviewed deceased patients of our study were 67.7% of elderly (considering elderly as >75 years old), 61.3% were critically ill patients and 19.4% with concomitant Diabetes Mellitus. The 38.7% of deceased patients had both risk factors, elderly and critically ill condition. The three risk factors have been seen in 6.45% of deceased patients.

Almost all deceased patients of the study (96.7%) had an ASA classification of III or IV, and only one patient (3.3%) had ASA II. There is a statistical significance between critically ill patient condition and ASA classification, the 57.9% of critically ill patients had an ASA IV and 42.1% had ASA III ($p=0.04$). Yi et al, reported a significant difference in the morbidity rate and surgical risk factors according ASA score. ASA I with 9.1% of morbidity rate and ASA III with 20%. [37]

All of deceased patient in the study had undergone surgical management. There were three types of surgery: 32.3% were operated by laparoscopic cholecystectomy, 61.3% of patients managed by open cholecystectomy and 6.5% of patients managed by percutaneous cholecystostomy. Ekici et al, reported that there is a significant difference in: the rate of surgery due to ACC, post-surgical complications and morbidity, conversion to an open surgery and hospitalization period, that were statistically higher in patients in the age group older than 60 years old [1]. P. Ignatius et al, reported that PC may be used as temporizing measure or as a definitive treatment for acute cholecystitis in critically ill patients. Laparoscopic cholecystectomy is the treatment of choice for acute cholecystitis in the Hospital of Lithuanian University of Health Sciences [40].

According literature, the most common cause of death after surgery is the multiple organ failure, usually most of these patients died later than the first week after surgery [36]. Most common causes of death in acute in the study were 54.8% by Multiple Organ Dysfunction Syndrome (MODS or MOF) and 45.2% by Sepsis.

The media of hospitalization period was 8 days (range 5-15). If we divided the deceased patients into two groups according to the year of death, we can find that there is a significance difference regarding hospitalization period ($p=0.03$). In the first group (2008-2013) the mean was 11.5± 12.2 days and in the second group (2014-2018) the mean was 9.3± 5.5 days.

The most common histopathological changes of acute cholecystitis related to death are: gangrenous gallbladder (48.4%), gallbladder perforation (29%), phlegmonous gallbladder (32.3%) and pericholecystic abscess (9.7%). According to literature, between 2% and 30% of patients admitted for acute cholecystitis develop gangrenous cholecystitis as a complication of the disease [49], gallbladder
perforation in approximately 2-11% of patients diagnosed with ACC [45] and about 15% of patients with AAC develops a perforation complication [48]. In our study the 48.4% of all deceased patients developed gangrenous gallbladder and 29% gallbladder perforation as a complication of acute cholecystitis. Ciftci et al reported a rate of conversion to open surgery of 43.7% in gangrenous cholecystitis and 28.1% in phlegmonous cholecystitis patients [30]. In our study, the only case of conversion from laparoscopic to open surgery was a case of gangrenous cholecystitis.
5. CONCLUSIONS

1. Women who are more than 75 years old has the highest mortality rate.

2. Mortality rate is significantly higher in the elderly patients of >75 years old.

3. From most common to fewer common causes of death in acute cholecystitis are: Multiple Organ Dysfunction Syndrome (54.8%) and Sepsis (45.2%).

4. According ASA classification, ASA III and ASA IV has the highest mortality rate. The 96.7% of deceased patients have ASA III or ASA IV.

5. The most common histopathological changes of acute cholecystitis related to death are: gangrenous gallbladder (38.7%), phlegmonous gallbladder (32.3%) and gallbladder perforation (29%).

6. Laparoscopic cholecystectomy is the treatment of choice for acute cholecystitis and PC may be used as temporizing measure or as a definitive treatment for acute cholecystitis in critically ill patients.
6. PRACTICAL RECOMMENDATIONS

After this study of causes of death in Acute Cholecystitis, it’s necessary to confirm that knowledge about the disease type and complications, can provide an early diagnosis of choledolithiasis or chronic cholecystitis, assign an appropriate treatment or surgical tactics before Acute Cholecystitis develops, and consequently, decrease the risk of comorbidities and also mortality rate.

Early surgery (<72h) for acute cholecystitis decreases the possibility of complications and has lower conversion rate in comparison to delayed surgery. Early cholecystectomy also reduces the hospitalization period. Video guided laparoscopic cholecystectomy is the treatment of choice in AAC and ACC, reducing the hospitalization period, morbidity and mortality. In elderly population (>75 years old), increases the comorbidities, mortality rate, and post-operative risk factors. PC has a beneficial role in high risk patient groups with comorbidities or severe disease, can be used as temporizing measure or as a definitive treatment for acute cholecystitis in critically ill patients.
7. REFERENCES


ANNEXES

- Questionnaire: Acute Cholecystitis: causes of death (2 pag).
## Patient code

<table>
<thead>
<tr>
<th>Date of birth</th>
<th>Date of admission</th>
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**Hospitalization period:**
- <7 days
- >7 days
- >2 weeks
- >1 month

**Time of onset:**
- <1 day
- 1-2 days
- 2-3 days
- > 3 days

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<td>&gt; 75</td>
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</table>

### Physiopathology

- Acute calculous cholecystitis (ACC)
- Acute acalculous cholecystitis (AAC)

### ASA classification

- I
- II
- III
- IV
- V

### Histopathological changes

<table>
<thead>
<tr>
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<th>NO</th>
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<tbody>
<tr>
<td></td>
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</table>

- Gangrenous gallbladder
- Gallbladder perforation
- Pericholecystic abscess
- Phlegmonous gallbladder

### Management

<table>
<thead>
<tr>
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- Conservative
- Surgical

### Type of surgery

<table>
<thead>
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- Laparoscopy (cholecystectomy)
- Laparotomy (cholecystectomy)
- Percutaneous cholecystostomy

### Conversion surgery

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- YES
- NO
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<td>Death during surgery</td>
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<td>☐</td>
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<tr>
<td>Death during post-operative period</td>
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</table>

<table>
<thead>
<tr>
<th>Risk factors (individually)</th>
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<th>NO</th>
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<tbody>
<tr>
<td>Critically ill</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Elderly (&gt;75 y.o)</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>☐</td>
<td>☐</td>
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<tr>
<td>Immunocompromised</td>
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<table>
<thead>
<tr>
<th>Direct cause of the death</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Multiple organ dysfunction</td>
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<td>Sepsis</td>
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<td></td>
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<td>Surgical complication</td>
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