

# Assessing the Burden of Choledochian Lithiasis and Cholangiocarcinoma in Patients Undergoing Endoscopic Retrograde Cholangiopancreatography, Using Disability-Adjusted Life Years

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## Abstract

Exact estimates of the current and future burden of gastroenterological pathology can support the national public health policy. In order to have a possible comparison between the impact and burden of some diseases, a series of health measurements were developed, simultaneously including morbidity and mortality. The aim of the study was to evaluate the burden of gastrointestinal pathology that requires therapeutic endoscopy, such as choledochian lithiasis and cholangiocarcinoma in a tertiary centre between 2019 and 2020. The scientific research was carried out as a retrospective study, intending to analyze the macroeconomic indicator-Disability-Adjusted-Life Year (DALY) in patients who underwent endoscopic retrograde cholangiopancreatography (ERCP), for the diagnosis of choledochian lithiasis or cholangiocarcinoma. The study included the cases diagnosed based on clinical, biological and imaging criteria. Our study showed that the values of DALY indicator are higher in men than in women. The DALY approach has a strong methodological framework and a firm theoretical grounding. It has been widely accepted by public health experts and employed to measure the global and regional burdens of the disease.

## Keywords

Endoscopy, Management, Cholangiopancreatography, Choledochian Lithiasis

## 1. Introduction

Endoscopic retrograde cholangiopancreatography (ERCP) consists of a combined, endoscopic and x-ray investigation that allows the radiological visualization of the bile and pancreatic ducts through the direct injection of the contrast substance subsequent to the Vater papilla catheterization, with a duodenoscope [1] [2]. This technique emerged more than 40 years ago in the US, when the first diagnosis of ERCP was reported by William McCune *et al.* in 1968, followed, a year later, by Itaru Oi in Japan. Although it was regarded with skepticism at first, due to the technical difficulties, but also to the potential complications that may occur post-ERCP, the technique began to be used worldwide [3] [4]. Since its introduction, ERCP went from a purely diagnosis procedure to a predominantly therapeutic one [5]. The number of ERCPS is constantly increasing, with the predominance of the therapeutic ones in the last 2 decades; thus, in the United States (US), there are performed about 450,000 ERCPS/year. In the United Kingdom (UK), the figures reach about 50,000/year, with only 13,000 ERCP/year less than China reported in 2006. Worldwidely, there are recorded 1.3 million ERCPS, certainly a figure that is well under the real need, which shows the small degree of accessibility of the general population. ERCP complications are divided into acute ones (acute pancreatitis, hemorrhage, retroduodenal perforation, acute cholangitis and cholecystitis) and chronic ones (stenosis of the external orifice of the choledochus, relapse of lithiasis, bacterial invasion of the bile duct). Information on the burden of choledochian lithiasis and cholangiocarcinoma can guide the authorities for establishing priorities in the field of prevention and control of these conditions.

ERCP is considered to be one of the most demanding and difficult technical procedures in gastrointestinal endoscopy. Until recently, the rate of complications was the only method to assess the result, because ERCP is associated with greater morbidity and mortality compared to other endoscopic procedures, such as colonoscopy and gastroscopy [6] [7] [8]. The ERCP equipment consists of endoscopes, catheters, guide wires, sphincterotomas, Dormia basket, plastic or metal prostheses, catheters for naso-bile or naso-gastric drainage, balloons and dilators, cytology brushes and biopsy punches and imaging equipment of highest quality [9] [10]. ERCP indications are choledochial lithiasis, the main indication, the benign stenoses of the common bile duct (CBD) that can be iatrogenic, postcholecystectomy or secondary to biliary surgery, malignant stenoses of CBD, neoplasms or intrahepatic metastases that produce dislocations of the intrahepatic bile duct [11].

Mortality does not provide a complete picture of the burden of the disease borne by individuals in different populations. The overall burden of the disease is assessed using the disability-adjusted life year (DALY), a time-based measure that combines years of life lost due to premature mortality (YLLs) and years of life lost due to time lived in states of less than full health, or years of healthy life lost due to disability (YLDs). One DALY represents the loss of the equivalent of

one year of full health. Using DALYs, the burden of diseases that cause premature death but little disability can be compared to that of diseases that do not cause death but do cause disability.

The basic idea expressed by DALY consists of the fact that the impact of a particular disease can be divided into the years of life lost as a result of premature death and the number of years lived with a disability (morbidity). The result obtained is usually expressed by a unique measure unit, which quantifies the years of healthy life lost due to a certain disease or infection. DALY is widely applied to estimate the burden of diseases at national, regional and global levels.

In this context, the purpose of the study was to evaluate the patients diagnosed and hospitalized for choledochian lithiasis and cholangiocarcinoma within the Emergency County Clinical “Sf. Spiridon” Hospital (Jassy, Romania) between 2019 and 2020, who underwent the ERCP procedure. The patients underwent clinical, biological and imaging investigations. There were analyzed the identification of the associated comorbidities, of post-intervention complications, as well as the mean number of hospitalization days. In order to have an objective image of the burden of these conditions in society, we calculated the economic indicator DALY for these patients.

## 2. Materials and Methods

Scientific research was performed as a retrospective study, aiming at analyzing the DALY macroeconomic indicator in patients who performed ERCP for the diagnosis of choledochian lithiasis or for cholangiocarcinoma. A DALY represents a lost year of healthy life. The option for this indicator was motivated by the simultaneous inclusion of morbidity and mortality indicators, providing a real measurement on the burden and impact of diseases on the general population.

Disability-adjusted life years (DALYs) are used globally to quantify the number of healthy years of life lost from the presence of a disease, disability, or injury. The burden of chronic, non-fatal health loss and early mortality is assessed separately and compared across various populations. Information on DALYs in the US and globally is often provided in Global Burden of Disease studies. Such information is used to inform healthcare providers about the impact of a health condition and guide interventions seeking to improve the health and life expectancy of a given population. Being that this time-based method measures the burden of a health condition in a population and compares it to a healthy population that reaches full life expectancy, the specific burden of common health conditions for middle-aged and older adults in the United States has yet to be calculated. More studies are required for understanding how aging is linked with the disease. Calculating the years lived with a disease (YLDs) and years of life lost (YLLs) from premature mortality will provide insights into the burden of common health conditions for the growing aging adult population. This information can help to identify which health conditions contribute most to the number of healthy years of life lost for the elderly, thereby informing how

healthcare providers and interventions prioritize treatment and prevention efforts. Such prioritization will help to guide health policy, and increase the quality of life and longevity for the elderly [12].

More studies used the DALY indicator to estimate the impact of biliary pathology in different countries or regions. The DALY indicator is a characterization of the impact of a disease, expressed by the number of life years lost as a result of premature death and the number of years lived with disability (morbidity). Thus, there is obtained a unique measure unit that quantifies the years of a healthy life lost due to a certain disease or infection. For the calculation of DALY, namely to determine the burden of the disease on the general population, only two characteristics are taken into account, age and sex, which are directly related to health, not taking into account the race, socio-economic status or level of education.

The study group includes 209 patients admitted to the Institute of Gastroenterology and Hepatology Jassy, “Sf. Spiridon” Hospital Jassy, between 2019 and 2020. The cases diagnosed based on clinical, biological and imaging criteria are included in the study. The criteria for patient selection in this study were patients with choledochian lithiasis and cholangiocarcinoma, regardless of the progression stage, psychologically and intellectually able to cooperate during the performance of investigations. All patients included in the study agreed to sign the “informed consent” form before undergoing the procedure.

Blood samples were collected, namely: full blood count, liver biological profile, kidney biological profile, blood sugar and coagulation samples. Every patient benefited from a complete clinical objective examination performed after the patient was asked about the disease history and the treatment taken at home. The following anthropometric indices were measured and calculated: weight, height, body mass index (BMI). The following medical investigations were performed: full blood count, liver function, kidney function, inflammatory syndrome, coagulation tests. All patients were evaluated by abdominal ultrasound, where the CBD diameter was measured. Also, during the research study, the patients were evaluated by abdominal CT, for tumor extension assessment. Only the cases with a complete dataset were included in the statistical analysis. The information obtained from the assessments of hospitalized patients for choledochian lithiasis or cholangiocarcinoma were introduced in a database using the Microsoft Excel program 15.20. The information was statistically processed through the IBS SPSS Statistics 24 for Mac OS program, the results being presented in the form of tables, charts and statistical tests.

The DALY indicator is widely applied to estimate the burden of diseases at national, regional and global level. For its calculation, we used the known formula, namely:  $DALY = YLD + YLL$ , where:

YLD (years lived with disability), years lived with disability or with change of behavior and/or motor ability. To estimate the YLD for a certain disease in a certain period of time, the number of cases in this period is multiplied by the

average duration of the disease and by the coefficient of disability impact, which reflects the severity of the disease on a scale from 0 (perfect health) to 1 (death).

For YLD calculation, for every patient in the studied group, we used the following items: the number of cases recorded during the study period was considered to be the number of patients included in the group, namely 50 patients with cholangiocarcinoma and 159 patients with choledochian lithiasis, the duration of the disease was considered to be characterized by the number of days of hospitalization, the coefficient of disease impact or severity on a scale from 0 to 1, we assessed it by the ratio between mortality and incidence, as presented in the specialized literature. The severity approach is drawn from a number of well-known theories of distributive justice asserting that the worst-off in society have special and legitimate claims. It is, however, not always clear what is meant by severity, and who the worst-off are. We may try to rank the patients that are worse-off with regard to their health status and relate this ranking to how much the treatment helps them. Yet there are different ways of approaching this situation. First, one can look at the current health status and expected improvement. From this angle, an improvement has more value if the current health status is worse but the expected improvements are the same. A second approach also considers the patient's health status.

For cholangiocarcinoma, in Europe the World Health Organization (WHO) reports indicate an incidence of 3.2/100,000 inhabitants in males and 5.4/100,000 inhabitants in females, and a mortality of 1.4/100,000 inhabitants in males and 1.9/100,000 inhabitants in females; therefore, the severity of the disease would be  $1.4/3.2 = 0.44$  in males and  $1.9/5.4 = 0.35$  in females. For biliary lithiasis, in Romania, scientific literature reports an incidence of 0.8/100 inhabitants, namely 80/10,000 inhabitants and a mortality of 15/10,000 inhabitants; thus, the severity of the disease is  $15/80 = 0.18$ .

YLL (years of life lost), life years lost as a result of premature deaths practically corresponds to the number of deaths caused by disease multiplied by the life expectancy indicator at the age at which death occurs.

For the calculation of YLL, for every patient in the studied group, we used the following elements: the number of deaths caused by the disease observed in the studied group, namely 17 (patients with cholangiocarcinoma) and 1 (patient with choledochian lithiasis).

### 3. Results

The statistical analysis was performed on a group consisting of 209 patients who underwent ERCP, of which 159 (76.1%) were diagnosed with choledochian lithiasis and 50 (23.9%) with cholangiocarcinoma.

#### 3.1. Patient Characteristics

The structure of the group according to sex highlights a slightly higher number in female patients (59.3% of cases) (**Figure 1**).

In general, the investigated patients belong to the elderly population, with an

average age of 65 years old (Figure 2).

The group was homogeneous in terms of the origin environment (Figure 3).

All the patients included in the study presented comorbidities. The most common comorbidities were represented by primary high blood pressure (25.4%) and liver steatosis (20.1%) (Figure 4).

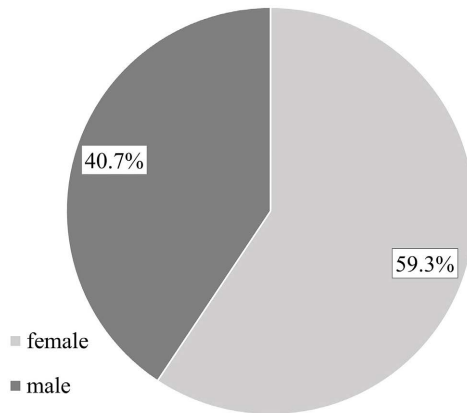


Figure 1. Patients distribution by sex.

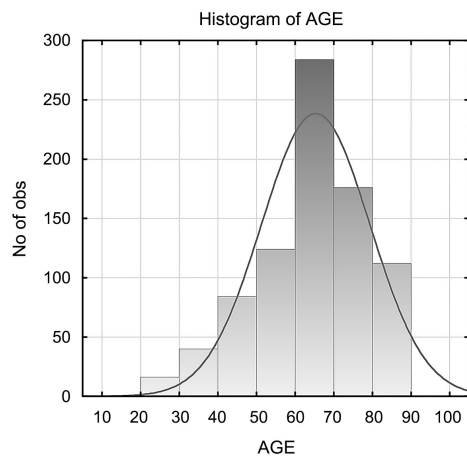


Figure 2. Patients distribution by age.

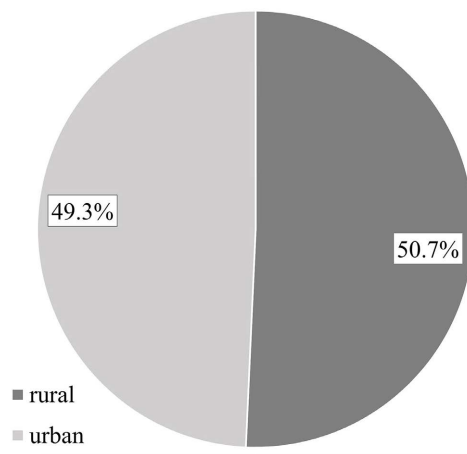
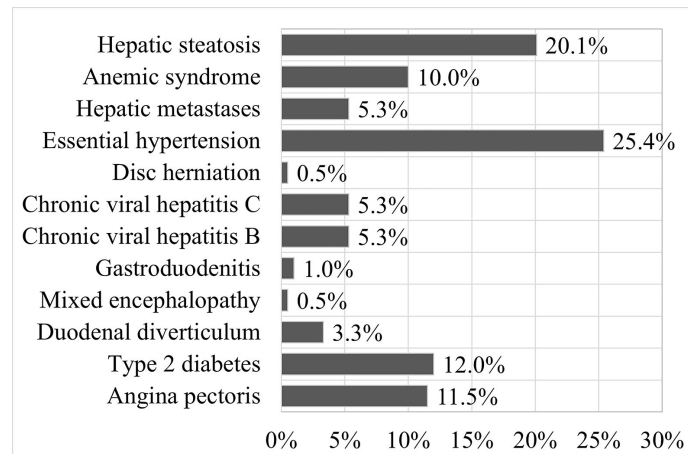


Figure 3. Patients distribution by residence area.



**Figure 4.** Patients distribution by comorbidities.

The comparative study of diagnosis comorbidities revealed statistically significant differences. In patients with choledochian lithiasis, the most commonly associated comorbidities were also primary high blood pressure (26.4%) and liver steatosis (23.3%). In contrast, among the patients with cholangiocarcinoma, there was observed an important percentage of associated complications, such as liver metastases (22.0%) as a consequence of the disease complications and anemic syndrome (20.0%) (**Figure 5**).

### 3.2. Laboratory Findings

Lower hemoglobin values were highlighted in patients with cholangiocarcinoma compared to those with choledochian lithiasis, both in the whole group (11.5 g/dl compared to 12.79 g/dl) and separately, in female patients (11.09 g/dl compared to 12.46 g/dl) and in male patients (11.95 g/dl compared to 13.33 g/dl) (**Figure 6**).

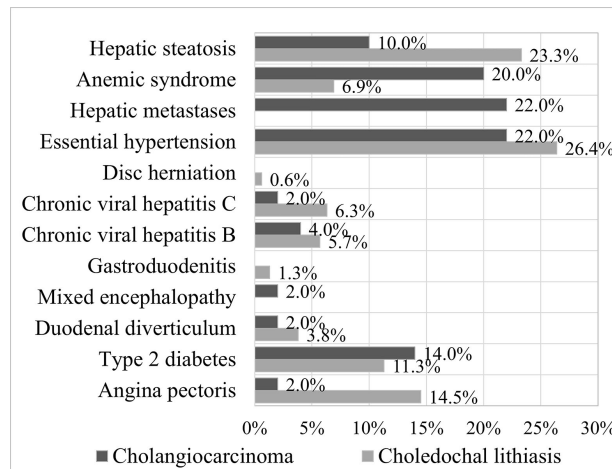
Total bilirubin was much higher in patients with cholangiocarcinoma compared to those with choledochian lithiasis (15.7 mg/dl compared to 3.46 mg/dl). In women, the increase of total bilirubin values was mainly highlighted in patients with cholangiocarcinoma (15.02 mg/dl) compared to the others (2.76 mg/dl).

We studied the progress of patients, in the whole group or comparatively on the two diagnoses. In the whole group, more than two thirds of the patients had a favorable progress (70.8%), about one fifth (20.6%) recorded complications and 18 patients (8.6%) deceased. In patients with choledochian lithiasis, 76.7% had a favorable progress, 22.6% presented complications and 0.6% represented deaths. In the case of the cholangiocarcinoma diagnosis, the favorable progress was recorded in 52% of the patients and 34% deceased (**Figure 7**).

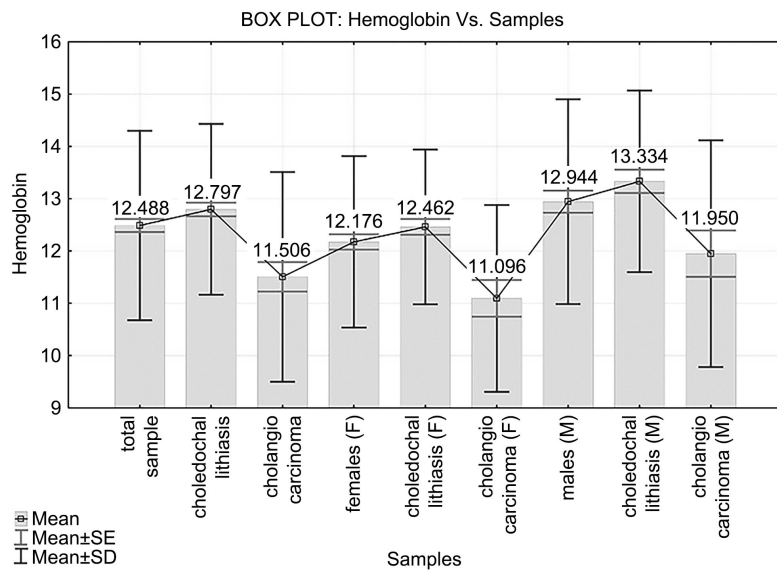
In the whole group, the most common complications recorded were papillary hemorrhage (30.2%), acute pancreatitis (27.9%) and pancreatic reaction (27.9%) (**Figure 8**).

The comparative study on diagnoses also highlighted statistically significant differences ( $p = 0.015$ ). Thus, papillary hemorrhage was observed in relatively similar percentages in patients with choledochian lithiasis (30.6%) and those

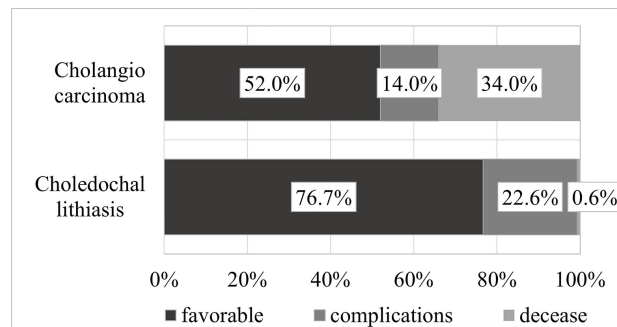
with cholangiocarcinoma (28.6%); in contrast, pancreatic reactions were observed only in patients with choledochian lithiasis, as well as upper digestive bleeding, but observed in a relatively low percentage (11.1%).



**Figure 5.** Correlation between diagnostics and comorbidities in the study group.

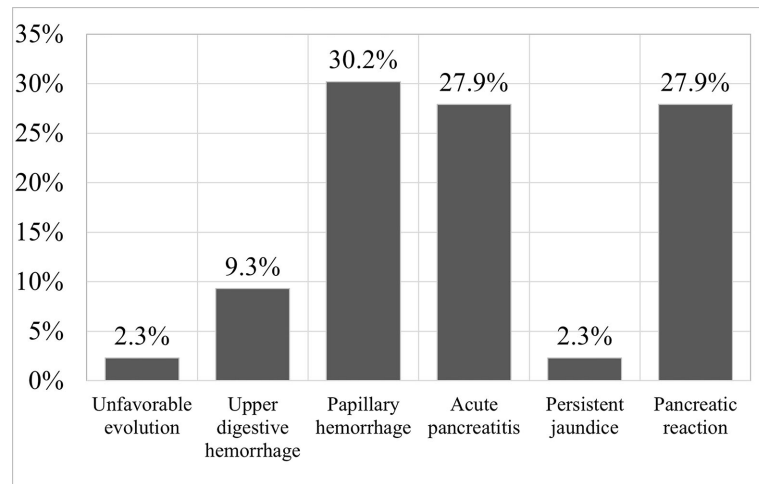


**Figure 6.** Evolution of hemoglobin value in all these cases.



**Figure 7.** Patients distribution by evolution.





**Figure 8.** Distribution of complications in the study group.

Patients with higher values of total bilirubin required a significantly larger number of hospitalization days. The average number of hospitalization days was significantly higher in patients with cholangiocarcinoma. The longest hospitalization periods were recorded in a patient having cholangiocarcinoma (26 days), but also in a woman with choledochian lithiasis (24 days). There was observed a positive, moderate and statistically significant correlation, between the level of total bilirubin and the number of hospitalization days in patients, identified during the analysis of the whole group ( $R = 0.302$ ). The situation is highly statistically significant and similar, reported both on the whole group of patients and separately by sex. In the whole group, more than two thirds of patients had a favorable progress. The comparative analysis on diagnoses, however, revealed statistically significant differences: the diagnosis of choledochian lithiasis was associated in the vast majority of cases with a favorable progress, while, in the case of the cholangiocarcinoma diagnosis, only half of the patients had a favorable progress.

The indicator of life expectancy at the age when death occurs was calculated based on the WHO reports, which indicate a life expectancy at birth for people of 75.3 years old in Romania (in 2017), higher in women (79.1 years old) and lower in men (71.7 years old). From this value we subtracted the age at which death occurred, in order to identify the patient's life expectancy at that time. In the whole group, the DALY indicator had the value of 344.437. In the whole group, the DALY indicator had the value of  $344.437 \pm 185.575$ . The separate analysis on sexes showed higher values of this indicator in men ( $387.900 \pm 190.876$ ), in comparison to women ( $303.637 \pm 192.528$ ). Most deaths were recorded in patients with cholangiocarcinoma. In this situation the DALY indicator is slightly higher than the similar value from the whole group, namely  $348.247 \pm 190.560$ .

#### 4. Discussion

The scientific research was represented by a retrospective study that analyzed the

characteristics of patients admitted to “St. Spiridon” Hospital, in the North-Eastern part of Romania, between 2019 and 2020, who underwent ERCP for the diagnosis of choledochian lithiasis or cholangiocarcinoma, also calculating the DALY economic indicator. The 209 patients included in the study were diagnosed according to clinical, biological and imaging criteria.

We also investigated the linear correlations between the clinical-biological parameters and the number of hospitalization days, in order to determine if there are any statistically significant correlations between these items; in case of identifying such influences, we detailed their direction and intensity by generating the appropriate linear regression model. Our findings should be used to inform healthcare providers and interventions seeking to prevent morbidity and extend life expectancy for patients with digestive diseases. Using DALY to guide healthcare policy will also help to improve quality of life during the aging period through a continuous progress of digestive disease prevention and treatment.

The performed studies showed that, for the calculation of DALY, the highest part is represented by the years that are lost due to mortality (deaths) and a lower number due to morbidity (disability). The estimates that are made regarding the burden of the disease and the causing risk factors are useful in the decision-making process. Unlike the worldwide model, in Romania, the first causes that determine the burden of the disease are: cardiovascular diseases, malignant tumors, mental and behavioral disorders, accidents, trauma, poisoning, central nervous system diseases, digestive diseases, respiratory diseases, infectious diseases, congenital malformations.

The burden generated by gastrointestinal pathology in society determined consequent concerns directed towards the formulation of healthcare policies leading to the improvement of the health state of the general population. The management approaches headed towards a measurement tool that accurately presents the size of the problem. Therefore, in order to have the possibility of comparing the impact and burden associated with these conditions, a number of health measurements were developed, simultaneously including morbidity and mortality, such as DALY. Through exact estimates given by objective measurement tools, the national public health policy benefits from an improvement reflected in the health state of the general population.

World Health Report 2002 identifies the most important 10 risk factors existing at global and regional level, depending on the burden of the disease it determines, assessed by DALY. In order of importance, these factors are represented by: high risk sexual behavior, high blood pressure, smoking, excessive alcohol consumption, lack of drinking water in the region, lack of hygiene or basic sanitation, iron deficiency, environmental pollution due to solid fuel, high cholesterol, obesity.

The correlation between the risk factors and the first ten conditions in the hierarchy of lost years, due to the disability and premature death, DALY is highlighted through the attributable fraction in the population, which shows the importance of a risk factor involvement in a certain disease. For example, for

highly developed countries, the first risk factors are smoking, high blood pressure, alcohol, high cholesterol, while in the DALY hierarchy, the first causes are: coronary heart disease, unipolar depression, cerebrovascular diseases and alcoholism. For medium developed countries, alcohol consumption, high blood pressure, smoking, malnutrition, obesity are the most common risk factors, and as DALY causes, there are specified: unipolar depressive disorders, cerebrovascular diseases, respiratory infections, trauma caused by road accidents. In underdeveloped countries, the ranking of the first risk factors is represented by: malnutrition, high risk sexual behavior, lack of drinking water and hygiene, solid particles pollution, and the first DALY causes are represented by: Human Immunodeficiency Virus (HIV)/ Acquired Immunodeficiency Syndrome (AIDS) infection, lower respiratory tract infections, diarrheic disease and childhood diseases.

DALY was used in studies in correlation with pathologies that create disability in the general population, such as stroke. Stroke is a leading cause of disability and death for adults that is also responsible for billions of dollars in healthcare costs. Keun-Sik Hong, in a review study, calculated the DALY lost in individual stroke patients and discussed its applications to acute stroke trials. Accordingly, the annual burden due to 64,688 ischemic strokes was estimated at 234,399 DALYs lost [13]. Although stroke has a high incidence in the general population, the DALY value was lower compared to the results of our study, which underlines the importance of therapeutic endoscopic intervention for gastroenterological pathology addressed in the study. Our DALY results for cholangiocarcinoma and choledochian lithiasis indicate more healthy years of life lost in adults. The fact that the DALY indicator was used for other pathologies from other specializations aroused our interest to apply it also in gastroenterological pathology and compare the results. A higher the DALY value for a certain pathology is mandatory that the financial and human resources of the respective hospital be directed in that direction.

May *et al.* investigated in a prospective cohort study the association between DALY and lifestyle and showed that choosing a healthy lifestyle such as non-smoking, maintaining a low BMI, being physically active, or consuming a healthy diet, results in a lower disease burden [14].

Future investigations should continue monitoring DALY for cholangiocarcinoma and choledochian lithiasis to assess advancements in digestive diseases treatment, prevention and care.

Some limitations should be noted. Those who were lost from follow-up or died may have had a health condition that was not recorded before this event, thereby creating underestimations for our results. In the study, we only included patients with choledochian lithiasis aged 23 years old and older and patients with cholangiocarcinoma aged 48 years old and older. Therefore, some participants may have had health conditions at younger ages before entering the study. Statistical tests of inference were not used for making comparisons between DALY estimates, because DALY is often used as a stand-alone statistic factor.

Also, YLD does not confirm that quality of life was compromised. Future investigations should examine the impact of a health condition on YLD.

## 5. Conclusions

The results of this study provide a detailed description of the burden of disease related to the gastrointestinal pathology that requires therapeutic endoscopy, such as choledochian lithiasis and cholangiocarcinoma in terms of mortality and disability, using data from studies and taking into account both acute episodes and chronic expressions of the disease.

The results obtained show that these data are important for the strategic planning of medical care and provision of intervention measures in time and space, especially for the working age groups, where the value of DALY indicator is significantly increased.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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