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***Asymptomatic cholelithiasis in adults: indications for
cholecystectomy***

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ASYMPTOMATIC CHOLELITHIASIS IN ADULTS: INDICATIONS FOR CHOLECYSTECTOMY

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List of Abbreviations

AC – Asymptomatic Cholelithiasis

ASMBS – American Society for Metabolic and Bariatric Surgery

BPD – Biliopancreatic Diversion

CC – Concomitant Cholecystectomy

EAES/ISS – European Association of Endoscopic Surgery and Italian Surgical Societies Working Group

EASL – European Association for the Study of the Liver

EM – Expectant Management

Emtree – Embase Subject Headings

GBC – Gallbladder Cancer

GIQLI – Gastrointestinal Quality of Life Index

HRQoL – Health-Related Quality of Life

LAGB – Laparoscopic Adjustable Gastric Band

LC – Laparoscopic Cholecystectomy

LRYGB – Laparoscopic Roux-en-Y Gastric Bypass

LSG – Laparoscopic Sleeve Gastrectomy

MeSH – Medical Subject Headings

NICE – National Institute for Health and Care Excellence

NIH – National Institutes of Health

PC – Prophylactic Cholecystectomy

PICO – Population, Intervention, Comparison, Outcome

PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses

SAGES – Society of American Gastrointestinal and Endoscopic Surgeons

SCD – Sickle Cell Disease

1. Abstract

Introduction: The predominantly benign natural history of asymptomatic cholelithiasis, along with high dissemination and low morbidity of laparoscopic cholecystectomy, has made the indications for cholecystectomy in patients with asymptomatic lithiasis controversial. Although most patients remain asymptomatic, it is believed that some subgroups of patients may be at greater risk of becoming symptomatic and developing complications, and as a result, prophylactic cholecystectomy may be indicated in these patients.

Objective: This work aims to review the essential details regarding indications for performing prophylactic cholecystectomy in patients with asymptomatic cholelithiasis.

Methods: The research was conducted within Pubmed and Embase between July and December 2021. Articles related to asymptomatic cholelithiasis and prophylactic cholecystectomy were included. Exclusion criteria were: certain types of articles (letters to the editor, case reports, questionnaires and reviews); full text unavailability; studies that included only symptomatic patients; pediatric patients; and cholecystectomy performed by surgical necessity.

Results: 589 articles were identified, of which 107 were selected after excluding duplicates and reading their abstract. After applying the exclusion criteria and performing a thorough reading of the remaining articles, 5 additional references of relevant guidelines to this topic were included. A total of 41 articles were used in this review.

Discussion: Indications for prophylactic cholecystectomy in patients with only asymptomatic cholelithiasis, along with main risk groups for symptomatic or complicated disease, were evaluated. Particular attention was paid to patients undergoing bariatric surgery or other abdominal surgery, cardiac and renal transplant recipients, patients with gallbladder polyps at increased risk of malignancy, patients with chronic hemolytic disease and diabetics.

Conclusion: Considering that the natural history of asymptomatic cholelithiasis is generally benign and that, despite being relatively safe, laparoscopic cholecystectomy is still attached to a standard morbidity, an expectant treatment is recommended for the general population with asymptomatic lithiasis. However, some controversy remains, as more recent studies consider that in subgroups such as: patients undergoing bariatric surgery or other abdominal surgeries, cardiac and renal transplant recipients, patients with gallbladder polyps

with increased risk of malignancy, and in patients with sickle cell disease, prophylactic cholecystectomy should be seriously considered. Regardless, until this date, clear indications for performing prophylactic cholecystectomy in these patients are still uncertain.

Keywords: asymptomatic cholelithiasis; prophylactic cholecystectomy; laparoscopic cholecystectomy; high-risk groups.

2. Resumo

Introdução: A história natural maioritariamente benigna da litíase vesicular assintomática, aliada à elevada disseminação e baixa morbidade da colecistectomia laparoscópica, tem vindo a tornar controversas as indicações para colecistectomia em doentes com litíase assintomática. Apesar da maioria dos doentes se manterem assintomáticos, acredita-se que alguns subgrupos de doentes possam ter maior risco de se tornarem sintomáticos e de manifestar complicações, pelo que a colecistectomia profilática pode estar indicada nestes doentes.

Objetivo: O presente trabalho pretende rever as particularidades relativamente às indicações para realizar colecistectomia profilática em doentes com litíase vesicular assintomática.

Métodos: A pesquisa foi realizada na Pubmed e Embase entre julho e dezembro de 2021. Foram incluídos artigos relativos a litíase vesicular assintomática e colecistectomia profilática. Os critérios de exclusão foram: certos tipos de artigos (cartas ao editor, relatos de casos, questionários e revisões); indisponibilidade dos artigos em formato completo; estudos que incluíram apenas doentes sintomáticos; pacientes pediátricos; e colecistectomia feita por necessidade cirúrgica.

Resultados: Foram identificados 589 artigos, dos quais 107 foram selecionados após a exclusão de duplicados e leitura do seu resumo. Depois de aplicados os critérios de exclusão e realizada uma leitura completa dos restantes artigos, 5 referências adicionais de *guidelines* relevantes para este tópico foram incluídas. Um total de 41 artigos foi utilizado nesta revisão.

Discussão: Foram avaliadas as indicações para colecistectomia profilática em doentes com litíase vesicular assintomática pura, assim como nos principais grupos de risco para doença sintomática ou complicada. Foi dada particular atenção aos doentes submetidos a cirurgia bariátrica ou outra cirurgia abdominal, recetores de transplante cardíaco e renal, portadores de pólipos da vesícula biliar com risco aumentado de malignidade, pacientes com doença hemolítica crónica e diabéticos.

Conclusão: Tendo em conta que a história natural da litíase vesicular assintomática é geralmente benigna e que, apesar de relativamente segura, a colecistectomia laparoscópica pode causar alguma morbidade, é recomendado um tratamento expectante na população em geral portadora de litíase assintomática. No entanto, ainda que exista

alguma controvérsia, estudos mais recentes consideram que em subgrupos como: pacientes submetidos a cirurgia bariátrica ou outras cirurgias abdominais, receptores de transplante cardíaco e renal, portadores de pólipos da vesícula biliar com risco aumentado de malignidade, e em doentes com anemia de células falciformes, a colecistectomia profilática deve ser seriamente considerada. Ainda assim, até ao momento, as indicações claras para a realização de colecistectomia profilática nestes pacientes são ainda uma incerteza.

Palavras-chave: litíase vesicular assintomática; colecistectomia profilática; colecistectomia laparoscópica; grupos de alto risco.

3. Introduction

The rising availability of abdominal ultrasonography for the investigation of abdominal symptoms has increased the diagnosis of asymptomatic cholelithiasis (AC). Considering that the management of this situation is controversial, the decisions require the need to consider the natural history of AC, as well as the risks of a cholecystectomy.¹

Laparoscopic cholecystectomy (LC) is usually a safe procedure, and regardless of risks such as injury to vessels or bowel, bile duct damage, and potential mortality associated,^{2,3} studies have shown that if performed in AC, it has a significantly lower risk of morbidity, when compared to that performed in symptomatic patients.⁴

The likelihood of developing AC is suggested to be heightened by risk factors such as older age, female gender, obesity and rapid weight loss, as well as diet and prolonged parenteral nutrition, specific drugs and diabetes.⁵

In the majority of AC patients, the progression rate to symptomatic disease is low, and they rarely experience complications.^{1,6} Moreover, they mostly develop symptoms before the occurrence of any complication.⁶ For this reason, prophylactic cholecystectomy (PC) has not been generally recommended in these patients.⁴

However, even without symptoms and despite being rare, complications such as acute cholecystitis and pancreatitis, which can be potentially fatal, can occur.⁴

Besides, some groups of patients have been shown to have a higher chance of becoming symptomatic, developing complications, or an additional risk of developing gallbladder carcinoma, and therefore, a PC may be indicated.¹ A clear risk stratification is still far from ideal and better identification of risk groups is needed.

Due to the lack of general agreement, with this systematic review we aimed to do an overview about the recommendations for PC in patients with AC.

4. Materials and Methods

Research within PubMed and Embase databases was made using Medical subject headings (MeSH)/Embase subject headings (Emtree) with the search equation: “asymptomatic cholelithiasis” OR “prophylactic cholecystectomy”, from July 18th to December 3rd, 2021.

In both search equations filters were defined concerning language edition (English, Portuguese and Spanish) and publication date (between 1989 and 2021).

The study followed the PICO structure: population, intervention, comparison and outcome (PICO). Population: adults with asymptomatic cholelithiasis. Intervention: cholecystectomy. Comparison: expectant management. Outcome: management of asymptomatic cholelithiasis regarding the indications for cholecystectomy in these patients.

Exclusion criteria were: article types - letters to the editor, case reports, questionnaires and reviews (with the exception of relevant guidelines on this topic); full text unavailability; research that included only symptomatic patients; pediatric patients and cholecystectomy performed by surgical need.

After the eligibility process, using the exclusion criteria, additional references of relevant guidelines on this research field were included.

5. Results

With the research equation 589 articles were found. After a primary selection was made by excluding the duplicates and screening the abstracts, there were 107 reports assessed for eligibility. After a secondary selection with some of the exclusion criteria, 5 additional references of relevant guidelines on this topic were included. A total of 41 articles were used in this review. A flow diagram of the research, based on the PRISMA (preferred reporting items for systematic reviews and meta-analyses),⁷ is illustrated in Figure 1.

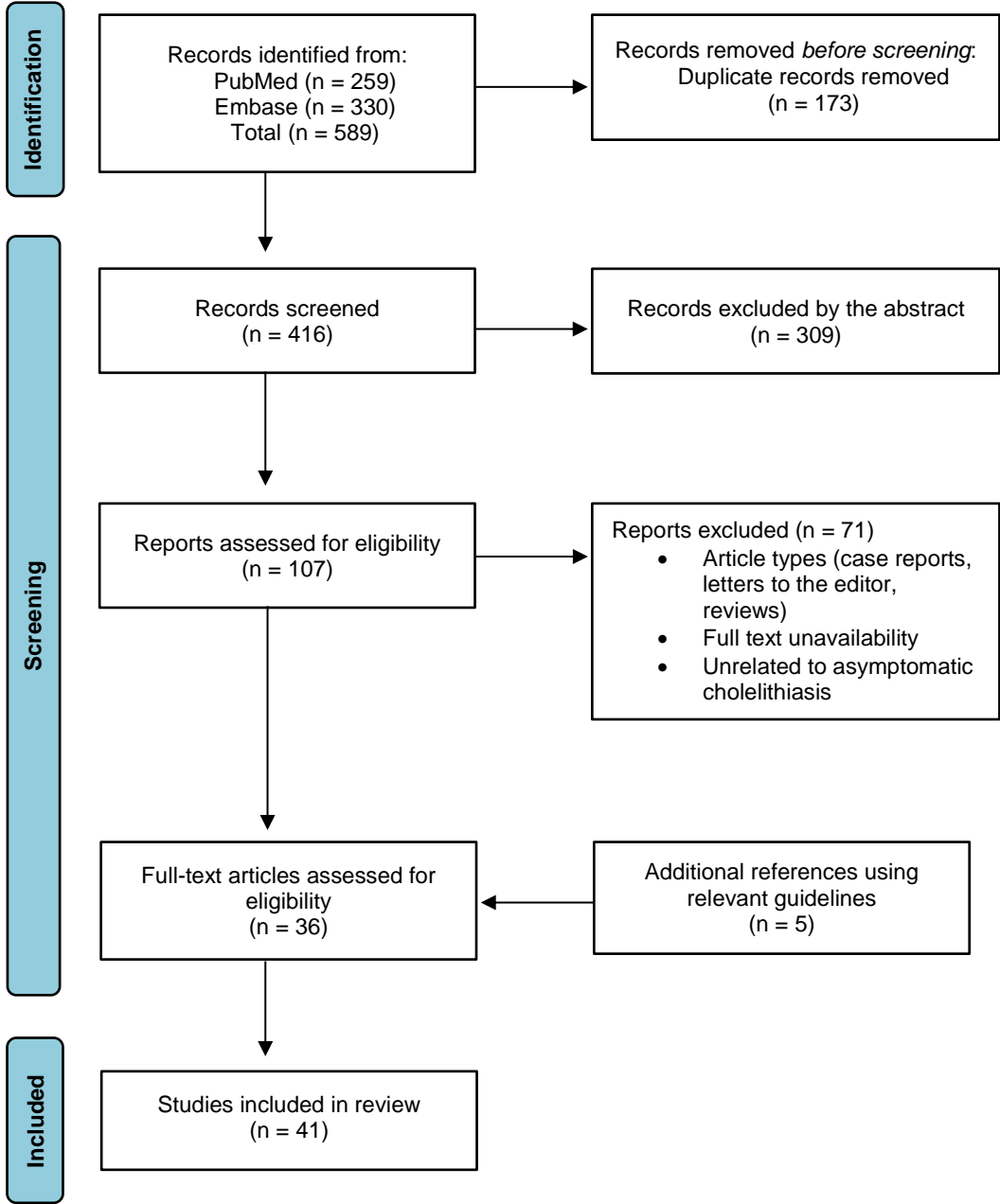


Figure 1. PRISMA flow diagram of the research representing the literature selection process

6. Discussion

6.1. Asymptomatic Cholelithiasis Patients

Even though near all patients with cholelithiasis remain asymptomatic, because of possible life-threatening complications *Yano et al.*,⁴ in 2003, compared the technique and outcomes of LC in both symptomatic and asymptomatic patients with cholelithiasis. They demonstrated that LC performed in asymptomatic patients has significantly lower risk of morbidity, lower conversion rates and lower operating time, when compared to that performed in symptomatic ones, and consequently, is a safe procedure for AC.

*Mentes et al.*⁸ suggests that although asymptomatic gallstones are not as distressing as symptomatic ones, uncomplicated LC improves the quality of life (evaluated by the Gastrointestinal Quality of Life Index - GIQLI) significantly in both groups of patients. However, others report that in patients with asymptomatic gallstones, in terms of health-related quality of life (HRQoL), the benefits of LC seem small relative to the risks, which supports a more conservative approach in this group.⁹ Either, it does not increase their life expectancy, since the risks of surgery outweigh the probability of complications.¹⁰

Most guidelines on gallstones management from different societies, published during the last decade agree, with a moderate level of evidence, that expectant treatment is justified in patients with AC.¹⁰⁻¹³ Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) guidelines, in 2010, claim that the indications for LC have not changed since the 1992 National Institutes of Health (NIH) *Consensus Development Conference Statement on Gallstones and Laparoscopic Cholecystectomy*,¹⁴ and defends that with few exceptions, AC is generally not an indication for LC.¹¹ As well, National Institute for Health and Care Excellence (NICE) guidelines accord that patients with AC without alterations on the gallbladder or biliary tree, do not need treatment unless they become symptomatic.¹²

Additionally, both European Association for the Study of the Liver (EASL), in 2016, and European Association of Endoscopic Surgery and Italian Surgical Societies Working Group (EAES/ISS) guidelines, in 2015, agree that routine PC is not generally recommended for patients with AC. However, they report some evidence that it might be considered or even advisable in some subgroups of patients as: cholecystectomy during another abdominal surgery including bariatric surgery, transplant patients, chronic hemolytic conditions, risk of gallbladder malignancy, among others.^{10,13}

For this reason, since there is roughly a general agreement that we should not perform LC systematically in asymptomatic patients without any other specific condition, we

decided to separate these subgroups in whom LC can be considered, from the general AC, and individualize each of them.

6.2. Asymptomatic Cholelithiasis in Patients with Other Specific Conditions

6.2.1. Bariatric Surgery

According to the American Society for Metabolic and Bariatric Surgery (ASMBS) recommendations on *management of gallbladder disease in patients undergoing minimally invasive bariatric surgery*, in 2020, both obesity itself and rapid weight loss are risks factors to the development of gallstones. This is explained mainly due to the increased secretion of cholesterol into bile.¹⁵

As will be shown below, there are studies with different rates of evolution from AC before any bariatric procedure, to symptomatic disease after surgery. For this reason, we decided to detach the types of bariatric surgery in different subgroups.

Biliopancreatic diversion (BPD) was not included in the present work since with our search equation no articles relative to this procedure were found. Likewise, the ASMBS abstains from making recommendations in patients undergoing BPD due to limited literature availability.¹⁵

6.2.1.1. Laparoscopic Sleeve Gastrectomy

Currently, there is no consensus on concomitant cholecystectomy (CC) during laparoscopic sleeve gastrectomy (LSG) in patients with AC.¹⁶

Conley et al.,¹⁷ in 2016, believed that cholelithiasis found before surgery had a different behavior from that induced due to weight loss after LSG. So, they compared both groups of patients and found that, although there was not statistically significant difference due to a small sample, in the group of patients who had AC present before LSG, symptoms occurred in only 5.6% of the patients, while in the group of patients in which gallstones developed after surgery 31% became symptomatic. This suggests that AC found prior to LSG tend to remain asymptomatic, and consequently, PC may not be needed, and these patients can be managed similarly to the general population. Contrariwise, another study developed with a bigger sample, in 2015, showed opposite results, with 9.3% of the patients

with AC prior to LSG and only 2.7% of the patients without preoperative cholelithiasis developing symptoms.¹⁸ Furthermore, symptoms and severity of the disease was more serious in the patients who had AC prior to the LSG.¹⁸ These results raise some doubts about whether expectant management (EM) is enough for these patients.

In more recent years, most studies suggest only an observational approach for AC diagnosed before LSG.^{15,16,19} *Sem et al.*,¹⁶ in 2021, reported that 97.6% of the cases remained asymptomatic during an average follow-up period of 17 months, with only 1 patient presenting symptoms after surgery. Thus, they do not recommend LC for asymptomatic patients. Also, *Yardimci et al.*¹⁹ suggests only observation for AC in patients who undergo LSG, since the majority of patients treated with an observational strategy will not require cholecystectomy, and also because time interval will allow a safer cholecystectomy after weight reduction.

ASMBS recommendations, in 2020, further advocate not to carry out PC in AC patients.¹⁵ Meanwhile, a more recent study, in October 2021, considers that LC is safe in all patients with preoperative gallstones since it has not found any difference in complication rates between concomitant LC and the bariatric procedure alone.²⁰ However, a possible limitation of this study is that both laparoscopic Roux-en-Y gastric bypass (LRYGB) and LSG were included, without separation of the results for each procedure.

6.2.1.2. Laparoscopic Roux-en-Y Gastric Bypass

Routine PC concomitant with LRYGB is also controversial.²¹ Some studies do not recommend LC in patients with AC before LRYGB,^{15,22,23} while others agree that LC is the best management for this group of patients.^{20,24,25}

Portenier et al.,²¹ in 2007, considers that either concomitant LC or an only observational approach might be acceptable in the management of patients with AC prior to LRYGB. They found that the group of patients with positive preoperative gallstones in whom the LC was not performed during LRYGB had an incidence of 17.3% delayed laparoscopic cholecystectomies, versus 9.8% in the group of patients with normal preoperative ultrasound findings. However, they also established that EM would avoid more than 82.3% of these patients to be submitted to an unnecessary procedure, and that delaying LC until patients have symptoms does not increase the risk of complications. Other authors reached similar conclusions, that a LC after LRYGB in individuals with prior AC does not have greater risks.²²

*Fuller et al.*²² suggests EM of patients with AC with prophylactic ursodiol® (ursodeoxycholic acid) following LRYGBP, given that despite the limited number of 13 patients with asymptomatic gallstones prior to the surgery, only 1 developed symptoms and required LC in 1 year follow-up.

Different conclusions were reached by *Tucker et al.*,²⁵ in 2008, in whose study a delayed LC was necessary in 18% of the patients with preoperatively cholelithiasis who did not undergo concurrent LC at LRYGB. More than 50% of patients with cholelithiasis or sludge developed complications, resulting in technically difficult surgeries or choledocholithiasis requiring additional procedures. Therefore, they propose that selective LC concomitant to LRYGB in patients with previous gallstones is safe, with low morbidity and no significant extension of surgery time and reduces the necessity for reoperation in these patients.

Recent studies, in 2021, have similarly concluded that performing a concomitant LC does not demonstrate higher rates of morbidity, extent of hospitalization or readmissions.^{20,24} Additionally, biliary complications related to the LC were significantly more frequent in the delayed LC group of patients.²⁴ As a result, they suggest that concomitant LC should be considered in patients with AC.^{20,24}

6.2.1.3. Laparoscopic Adjustable Gastric Band

O'Brien et al.,²⁶ in 2003, advocate not to perform LC in the same session of laparoscopic adjustable gastric band (LAGB), and defends an observational approach. According to their study, the management of AC with LC in patients with gallstones found on a routine preoperative ultrasound would have generated additional surgeries in a high percentage of patients without evidence of clear benefit, and also, higher costs.

Moreover, according to the ASMBS guidelines, LAGB procedure results in a lower percentage of symptomatic gallstones than LRYGB or LSG. Thus, they recommend not to perform LC in patients with AC before LAGB.¹⁵

6.2.2. Other Abdominal Surgeries

Several studies since 1989 suggest that, in patients with AC, incidental cholecystectomy during an abdominal surgery for gallbladder unrelated conditions should be performed, unless there are contraindications.^{13,27-31}

Bragg et al.,²⁷ in 1989, analyzed the outcome of 68 patients with AC undergoing laparotomy for unrelated conditions and realized that 54% of the patients became symptomatic, 22% required early cholecystectomy within 30 days of surgery, and 70% within 6 months. They also concluded, that patients who needed mechanical ventilation, blood transfusions, parenteral nutrition and those who delayed to reintroduce enteral nutrition were more likely to require cholecystectomy. As a result, they propose that CC adds minimal risks and should be performed.

Similarly, CC with colorectal surgery in patients with AC is also recommended.^{28,31} *Juhasz et al.*²⁸ showed that performing cholecystectomy did not increase morbidity after surgery, whereas there was a high risk of this patients becoming symptomatic in long-term. Other authors, in 2015, reached almost identical conclusions in colorectal cancer surgery.³¹ In their study patients with AC were divided in 2 groups: one that did undergo concomitant cholecystectomy and other that did not. They showed that 8.6% of colorectal cancer patients who did not undergo CC developed later biliary complications. In addition, this study revealed that, although the mean surgery time was higher in the CC group, overall morbidity rates were similar in both groups. Furthermore, the rate of perioperative biliary complications in cholecystectomy group was low (0.7%).³¹

Also, in patients with gallstones undergoing primary subtotal resection of the small intestine, CC is advisable to be performed if these patients require chronic parenteral nutrition, due to a high risk of developing acute cholecystitis.³⁰

An interesting study developed by *D'Angelo et al.*²⁹ suggests that in patients with AC submitted to uncomplicated abdominal aortic aneurysm repair, CC should be performed. Data from their study showed that patients who underwent CC did not have significant difference in operative time. In addition, the group of patients who did not undergo cholecystectomy had an increased morbidity in the postoperative period, with statistically significant biliary tract complications, while patients with CC did not develop any.

In more recent years, the 2015 EAES/ISS guidelines on LC agree, as well, to perform LC in AC patients during other abdominal procedures, as long as no prosthetic material is used.¹³

6.2.3. Transplant Recipients

As will be seen below, different solid organ transplantations may have different approaches for AC. For this reason, we decided to detach different types of transplants in different subgroups.

Due to the eligible articles included in our review, only renal and cardiac transplants were addressed.

6.2.3.1. Renal Transplant

There are controversial opinions whether LC should or not be performed in patients with AC who will undergo renal transplant, and in patients with AC diagnosed post-renal transplantation. While some studies propose EM in patients qualified for renal transplantation,^{13,32-34} others believe that PC is beneficial in prerenal transplant patients.^{35,36}

In a study developed by *Greenstein et al.*,³² from 15 patients with AC submitted to renal transplant, 13 (87%) have remained asymptomatic postoperatively. Similar data was reached in another study in 2005, in which from 20 patients with AC managed expectantly without cholecystectomy before transplantation, none developed biliary tract symptoms.³³ These studies suggest that AC is not related to increased morbidity after renal transplantation, and that, as in the general population, the risks associated with AC do not appear to justify pretransplant cholecystectomy.^{32,33}

Also, the EASS/ISS guidelines, from 2015, agree that an EM should be taken in renal transplant recipients.¹³

However, *Meka et al.*,³⁵ in 2008, proposes LC to all prerenal transplant patients diagnosed with gallstones. In their study they compared the rate of complications between 2 groups of patients: one with AC who have been submitted to pretransplant LC, and other with patients who underwent cholecystectomy due to gallstone disease post-renal transplantation, who have not been previously cholecystectomized. The results showed that the group submitted to elective LC had less morbidity, mortality and, graft loss. This suggests that EM of cholelithiasis in immunosuppressed transplant recipients can have increased complications,³⁵ and that LC might be benefic in prerenal transplant patients identified with AC.^{35,36}

Other study, published in 2005, recommends PC only for AC patients with risk factors as microlithiasis or scleroatrophic cholecystitis, even though 39% of the patients managed without pretransplantation cholecystectomy have developed biliary tract symptoms within 5.5 years of the transplant.³⁷

In patients with renal transplants, the rate of complications and morbidity due cholecystitis seems to be higher than in general population, most likely because of immunosuppression and its masking effects.³⁸ For this reason, and because of increased risk of cholelithiasis in patients taking cyclosporine, *Sutariya et al.*³⁸ recommends that in patients with AC post-transplant, LC should be performed.

6.2.3.2. Cardiac Transplant

A study developed by *Menegaux et. al.*³⁹ suggests that cardiac transplant recipients with cholelithiasis should be submitted to LC postoperatively, independently of their symptomatic status. In their study they noticed that in both groups of patients submitted to open cholecystectomy and LC after cardiac transplantation, no significant complications occurred. Therefore, it should be performed after the transplant, as oftentimes a poor cardiac function does not allow pretransplant cholecystectomy.

A much larger study, conducted in 2013, analyzed 1687 cardiac transplant recipients who underwent cholecystectomy. It denoted that overall inpatient mortality was higher in urgent (3,6%) versus elective cases (0%), with statistical significance. Also, urgent cholecystectomies and open cholecystectomies had higher complication rates when compared with laparoscopic or elective procedures. The predictors of inpatient mortality were urgent admission, open cholecystectomy, and complicated gallstone disease, all statistically significant. As a result, they recommend performing LC in all stable patients with cholelithiasis submitted to cardiac transplant, including asymptomatic ones, to prevent the progression to complicated disease, and the associated morbimortality.⁴⁰

Similar conclusions were reached by *Kao et. al.*,³⁴ in an interesting study using a decision analysis software, based on estimates derived from the literature, to compare pretransplantation PC, post-transplantation cholecystectomy, and EM of incidental cholelithiasis. For patients with diagnosed AC qualified for cardiac transplant the best management conduct was prophylactic post-transplantation cholecystectomy since this strategy had an anticipated mortality of 5 deaths per 1000 patients, versus 80 per 1000 for pretransplantation cholecystectomy and 44 per 1000 for observational approach. Although

these decision model estimates do not always reflect true clinical situations, this study suggests that PC should be performed post-cardiac transplantation, but after the initial recovery period of increased immunosuppression, and before these patients become symptomatic.

Also, PC after cardiac transplant is believed to be cost-effective in patients with AC, due to the reduction on mortality rates.^{10,34}

6.2.4. Malignancy Risk and Gallbladder Polyps

A study conducted by *Jung et al.*,⁴¹ in 2009, to investigate the utility of cholecystectomy in patients with AC for early diagnosis of dysplasia or cancer, showed that the prevalence of dysplasia or cancer in patients with AC was statistically significantly higher than in those with symptomatic ones. However, further analysis after excluding the patients with polyps denoted that, although not statistically significant, no cases of dysplasia were found in the asymptomatic group. Consequently, they suggest that performing PC in patients with AC without polyps, to prevent gallbladder cancer (GBC), does not seem to be beneficial.

Another study compared the clinical differences between individuals with cholelithiasis and gallbladder polyps together, and patients with isolated polyps. They concluded that, even though there was no significant difference in polyps size between the two groups, patients with gallbladder polyps and concomitant cholelithiasis with characteristics as thickened gallbladder wall and increase in polyp size, can have a higher risk of malignancy, and PC may be considered.⁴²

The EASL clinical practice guidelines on *the prevention, diagnosis and treatment of gallstones*, from 2016, also recommend considering LC in patients in asymptomatic cholelithiasis and concurrent gallbladder polyps in case of growing polyps, but also in polyps with 6-10 mm. In gallbladder polyps ≥ 1 cm LC should be performed independently of the presence of gallstones due to an increased likelihood of being adenomas or even carcinomas, and in polyps ≤ 5 mm it should not be performed since there is a low risk of malignancy.¹⁰

A study developed in a high incidence GBC country, as Pakistan, showed a statistically significant positive correlation between gallbladder cancer and gallstones >1 cm, solitary stones and age >55 years. Consequently, they suggest performing an early PC in

this high-risk group, so that it may reduce the progression of GBC in countries with high incidence of this carcinoma.⁴³

However, these conclusions should not be extrapolated for Western countries, where EAES/ISS guidelines agree that there is no indication for PC, as the incidence of GBC in patients with AC is <1%.¹³

6.2.5. Chronic Hemolytic Condition: Sickle Cell Disease

In patients with sickle cell disease (SCD) and AC, a vaso-occlusive crisis can mimic biliary complications from gallstones, what makes difficult to reach a definitive diagnosis and the right approach.^{10,44} Moreover, cholelithiasis is much more prevalent in individuals with SCD than in general population, reaching up to more than 80% of people older than 30 years.⁴⁵

*Muroni et al.*⁴⁴ analyzed the outcomes of laparoscopic cholecystectomies performed on SCD patients with both symptomatic and AC. The results showed less postoperative complications for the AC group submitted to PC, as well as less SCD related morbidity and less hospital stay. Accordingly, the authors suggest that PC, in AC patients with SCD, is a safe procedure that can prevent emergency surgeries, with worse outcomes, for acute complications of gallstones.

Also, the EASL guidelines propose to perform LC in AC patients with SCD at the time of splenectomy, or during other abdominal surgery, to prevent difficulties in the diagnosis during sickle cell crises.¹⁰

6.2.6. Diabetes Mellitus

Favero et al.,⁴⁶ in 1994, developed a study to evaluate the natural history of cholelithiasis in patients with non-insulin-dependent diabetes. They divided the patients with gallstones into two groups: a symptomatic group and an asymptomatic group, and noticed that the rate of asymptomatic patients who presented with biliary symptoms during the follow-up was 14.9%, and with complications was 4.2%. As a result, they propose that, since the natural history of non-insulin-dependent diabetes mellitus patients with AC may not be different from the general population, PC may not be necessary.

Also, more recent guidelines from the EASS/ISS recommend that PC should not be performed in diabetic patients with AC.¹³

7. Conclusion

Having into account that the natural history of asymptomatic cholelithiasis is generally benign, with rare complications, and that symptoms usually precede the development of severe complications, the management of asymptomatic gallstones in the general population is suggested to be expectant, with no benefits from performing a prophylactic cholecystectomy.

Nonetheless, even though there is some controversy, in some subgroups of patients that have been shown to have a higher risk of becoming symptomatic or developing complications, such as patients submitted to bariatric surgery or other abdominal procedures, cardiac and renal transplant recipient patients, patients with gallbladder polyps with increased risk of malignancy or patients with chronic hemolytic conditions, prophylactic laparoscopic cholecystectomy should be considered.

Above all, patients need to be informed about the natural history of asymptomatic gallstones, as well as the potential morbidity and mortality of a cholecystectomy, and their preferences should be taken into consideration, as the surgical approach is still an individual decision.

Limitations of the present work included: the use of general MeSH terms, in order to accommodate more relevant literature, which may have led to the non-inclusion of studies on more specific topics; the need to add relevant guidelines on this research field so that a more complete bibliography could be considered; data found from different populations sometimes made it difficult to establish comparisons; and focusing mainly on the more prevalent high-risk populations with asymptomatic cholelithiasis presented in the selected articles.

In conclusion, considering the natural history of asymptomatic cholelithiasis, prophylactic laparoscopic cholecystectomy should not be advised for the general population, but instead, selectively performed in high-risk subgroups.

There have been no randomized controlled trials assessing the benefits of cholecystectomy in asymptomatic patients. Therefore, in the future, additional research must be conducted so that a more consensual approach of patients with asymptomatic cholelithiasis can be reached. Also, the desirable evolution of the laparoscopic cholecystectomy technique will most certainly lead to less morbidity, and so, the indications for prophylactic cholecystectomy are expected to expand. Until now, clear indications for prophylactic cholecystectomy in these patients are still an uncertainty.

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