Lights and shadows in predicting choledocholithiasis: Opportunities for future research

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Abstract
Secondary choledocholithiasis is a disease of high prevalence that involves diagnostic and treatment challenges; it implies a high use of resources and economic costs. There are significant knowledge gaps related to clinical prediction models, risk group classification, and patient treatment in secondary choledocholithiasis cases. Those gaps include diagnostic performance, variables, and risk thresholds, as well as cost-effectiveness for the use of non-invasive and invasive resources, and their application in special population groups. This study analyzes those knowledge gaps and outlines a guideline that could lead future research.

Keywords
Choledocholithiasis, Choledocholithiasis risk, Diagnostic, Prediction model, Thresholds.

INTRODUCTION

Cholelithiasis is a globally common surgical entity affecting between 10% and 15% of the general population(1). One of its typical complications is choledocholithiasis, defined as stones in the common bile duct (CBD). There are two forms of choledocholithiasis: primary and secondary. On the one hand, primary choledocholithiasis refers to the on-site formation of stones in the CBD; this form corresponds to 10% of cases and is more frequent in Asian countries(2). On the other hand, the secondary form (90%) occurs by the direct migration of stones from the gallbladder. This type of choledocholithiasis has a variable manifestation between 4.6% and 20.9% of patients with cholelithiasis in different contexts(1,3-6). The disease prevalence and burden in Colombia are unknown, although some studies estimate that about 11.9% of patients admitted to the emergency services with acute cholecystitis have choledocholithiasis(7).

Secondary choledocholithiasis represents a tremendous economic burden for health care systems. For example, in the United States, it costs approximately $6.6 billion annually, including the cost of cholecystectomy as a definitive treatment(8). Some studies available in Colombia report on the cost of this disease for institutions, but little is known about its economic impact on the health care system(7,9,10).
La predicción de coledocolitiasis: oportunidades para la investigación futura

La predicción de coledocolitiasis ha experimentado cambios notables en los últimos años, principalmente en relación a las variables del paciente, biomarcadores y técnicas diagnósticas. La precisión de la predicción se ve afectada por la interpretación de estudios previos, que han utilizado métodos y criterios de diagnóstico con validez variable. En el presente ensayo se analizan y discuten los resultados de varios estudios en relación a la predicción de coledocolitiasis, con el objetivo de identificar las áreas de oportunidad para la investigación futura.

**VARIABLES INCLUIDAS EN LA PREDICCIÓN Y MODELOS DE INTERACCIÓN**

Típicamente, en la predicción de coledocolitiasis se han considerado variables como la edad, el sexo, el estado de salud general, así como variables biomédicas como el tiempo de sangrado, la bilirrubina y la alanina-aminotransferasa. Sin embargo, se ha evidenciado que la combinación de variables biomédicas y clínicas puede mejorar la precisión de la predicción. Por lo tanto, es importante identificar las variables más relevantes y su interacción en diferentes contextos clínicos.

**LA VALORACIÓN DE LA MODALIDAD ASGE**

El modelo de ASGE es uno de los más utilizados para la predicción de coledocolitiasis. Este modelo clasifica a los pacientes en tres grupos de riesgo: bajo, medio y alto. Sin embargo, el modelo de ASGE ha sido criticado por su falta de generalización y por no ser aplicable en todos los contextos clínicos. Además, el modelo de ASGE no considera las variables clínicas, lo que limita su exactitud.

**LA VALIDACIÓN DE LOS MODELOS**

El ensayo resalta la necesidad de validar los modelos existentes y crear nuevos modelos que sean aplicables en diferentes contextos. El diseño de modelos precisos y válidos requiere una cuidadosa validación de los resultados obtenidos en diferentes estudios. Además, es importante considerar la generalización de los modelos y su ajuste a diferentes grupos de pacientes.

Este estudio busca identificar las áreas de oportunidad para la investigación futura en la predicción de coledocolitiasis, con el objetivo de mejorar la precisión de la predicción y optimizar el tratamiento de la enfermedad.
Characteristics (ROC)\(^{(7)}\), consistent with results in its external validation\(^{(13)}\). Other studies conducted in Lithuania and Saudi Arabia report similar findings\(^{(13,22)}\). New proposals, especially in the last year (2021), have sought to improve certainty in diagnostic prediction. Chisholm et al introduced a model in 2020 based on multivariate analysis in a specialized referral center to reduce the number of false positives (patients undergoing non-therapeutic ERCP) and false negatives (patients undergoing cholecystectomy with choledocholithiasis)\(^{(19)}\). Good discrimination was obtained from approximately 80% of the population, with failed ERCP rates of 22% versus 42% for ASGE for the high-risk group and false-negative occurrence of 1.4% for the low-risk group. Twenty percent of the population in the intermediate group required additional diagnostic studies.

Building on the limitations above, new studies can focus on:

- Objectively assessing the interaction of the variables within the ASGE model. Studies of this type can help determine, using statistical methods, the best cut-off points for each variable and their relative weight within the model. This analysis can inform the operating characteristics of the model based on original empirical studies.
- Validating the available models in different populations. Given their growing use and wide acceptance in multiple practice contexts, there is a latent need to validate the ASGE and ESGE models.
- Comparing the operating performance of the models in terms of their operating characteristics.
- Determining the performance of the models in clinical situations that may affect the behavior of the variables, such as in cases of acute cholecystitis or advanced age, which have been shown to affect the parameters of biochemical markers or the accepted average diameter of the bile duct, respectively.

**CRITERIA AND MECHANISMS FOR DETERMINING RISK THRESHOLDS IN AVAILABLE MODELS**

The problem of adjusting the risk thresholds within the models is defining which patient falls into the high, medium, or low-risk groups. So, for instance, the stricter the high- or low-risk criteria, the fewer patients will be included in these groups, affecting the number of patients in the uncertain or medium risk zone. Therefore, the definition of thresholds can impact diagnostic and treatment resources. Good discrimination of risk thresholds should seek to reduce the number of patients taken to non-therapeutic ERCP, given the burden of morbidity of the procedure, and accurately distinguish patients who require additional diagnostic studies from those who can be safely taken to surgery. These models must have the ability to adapt to each clinical scenario, considering their available staff, experience, therapeutic resources, and cost-effectiveness.

Overall, the proposed prediction models show adequate global operating characteristics in the discrimination of risk groups. The ASGE model has shown a diagnostic sensitivity in the high-risk group of 90% to detect choledocholithiasis, while the low-risk group is close to 5%\(^{(1,3,10)}\). National validations have provided similar data\(^{(23)}\); however, the intermediate-risk groups remain a concern due to low diagnostic sensitivity, between 26% and 49.5%\(^{(1,18,23)}\). The number of patients in this group under the current risk distribution causes most patients to go through additional pre-surgical diagnostic studies, with unknown outcomes such as an immediate increase in care costs, delay in therapeutic management, and increased complications derived from a more extended hospital stay\(^{(27)}\).

The thresholds, therefore, affect the model’s overall functionality and the use of diagnostic tests, especially in the intermediate and low-risk groups. These aspects are essential when deciding on diagnostic methods, especially non-invasive ones. The latter, specifically EUS and NMRC, demonstrate a sensitivity of 97% and 87% and specificity of 90% and 92%, respectively\(^{(28)}\). Currently, they are widely used diagnostic tests, especially in the medium-risk group or in the uncertain zone, where invasive methods such as ERCP are not justified due to their associated risks (5%–10%)\(^{(13)}\). Clinical trials have shown that EUS and NMRC have a performance comparable to ERCP in diagnosing choledocholithiasis\(^{(29,30)}\). Even though EUS has a slightly higher sensitivity for diagnosis than NMRC\(^{(31)}\), its applicability is limited by its low availability and operator-dependency\(^{(29,32)}\).

Intermediate risk can impact the performance of diagnostic precision methods such as EUS and NMRC. In high risk, a probability of a false positive that is not insignificant is assumed, which is reported on current models by up to 50%\(^{(27)}\), indicating an invasive procedure associated with risk such as ERCP with non-therapeutic purposes. Therefore, many schools today consider it relevant to take on the cost of confirming the high probability of choledocholithiasis determined by prediction models with diagnostic methods such as EUS in certain situations, including an increased risk of post-ERCP pancreatitis, pregnancy, or simply the need to zero the possibility of a non-therapeutic ERCP. What levels are we willing to assume as non-therapeutic ERCP? What percentage of patients undergoing surgery with choledocholithiasis is adequate? These questions persist and must be adjusted to each clinical context.

Building on the limitations above, new studies can focus on:

- Adapting the risk thresholds according to the risk-benefit of diagnosing all patients to reduce the number of false positives in high risk and increase the percentage.
of patients who can be safely taken to surgery without additional diagnostic studies.

- Dynamizing the risk thresholds of the ASGE model and assessing its impact on clinical diagnosis in specific population groups, providing adjustment alternatives to their clinical contexts.

The need for prospective clinical studies that validate the changes in the current structures and confirm and dynamize the models in their clinical settings becomes necessary in elaborating this topic and bridging knowledge gaps.

**APPLICABILITY OF GENERIC PREDICTION MODELS TO SPECIAL POPULATIONS**

Another important point with limitations in the approach of current risk models has to do with their application to particular groups of patients: older adults (> 65 years), history of cholecystectomy, primary cholelithiasis, biliary obstruction of malignant origin, and pancreatitis of biliary origin. Diagnostic prediction scales designed for patients with secondary cholelithiasis have been routinely applied to these groups. However, the validation of the models available is limited in these particular groups. The adaptation of prediction models to groups for which they have not been developed or validated can affect their operating characteristics in terms of false negatives and positives, affecting the use of resources and diagnostic tests. For example, distinguishing biliary obstruction by malignancy versus benign disease is not straightforward. Multiple clinical and laboratory predictors are altered in both entities, even with invasive diagnostic elements such as ERCP and EUS. Differential risk determination is necessary, mainly identifying extra-hepatic cholestasis due to biliopancreatic malignancy versus benign biliary pathology.

Patients over 65 years of age are also in this category. On the one hand, this group of patients, which is increasing due to the aging rate of the population, has unique features, such as a higher prevalence of cholelithiasis, an increased risk of complications, and pathophysiological changes in stone production. These factors make it necessary to adjust the generic models to each group of patients to provide safe and effective treatment and reduce the risk of associated complications. On the other hand, the information and its use in primary cholelithiasis are limited. Some models in secondary cholelithiasis have been adapted to the primary cholelithiasis approach. Nonetheless, their yield is suboptimal, as these entities have a different pathophysiological pathway with a high recurrence rate (up to 41.7%)..

Based on these limitations, new studies may focus on adapting and assessing the validity of predictive models for secondary cholelithiasis in these particular groups or create new specific models from empirical studies in special populations.

**IMPACT OF PREDICTION MODELS ON THE COST-EFFECTIVENESS OF DIAGNOSIS AND TREATMENT**

Regarding the cost-effectiveness of the diagnosis, the discussion about the impact of the models on the cost-effectiveness derived from non-invasive diagnostic tests (NMRC and EUS) and invasive tests (ERCP) is still valid. Cost-effectiveness analyses have shown that the routine use of NMRC or EUS in intermediate-risk patients reduces the care costs related to non-therapeutic ERCP and its complications. The comparison about the usefulness of non-invasive tests suggests that EUS offers better diagnostic yield; nonetheless, when including the costs related to the procedure and comparing them with those of the NMRC, the latter appears to be more cost-effective.

The approach to the cost-effectiveness of risk stratification is diverse. Kang et al demonstrated the ASGE’s model effectiveness in a population over 55 years of age, compared with the routine use of NMRC in all patients with suspected biliary obstruction, including malignant obstruction. However, their results have been re-evaluated due to flaws in the model’s sensitivity analysis and use in different types of populations.

Other approaches to cost-effectiveness in local studies have revealed the suboptimal yield of the ASGE model compared to national models. However, data are limited to the impact on the immediate cost for institutions and lack evaluations at the health system level.

Additionally, as a secondary objective of some clinical trials, the cost-effectiveness of endoscopic management in two stages (ERCP + delayed laparoscopic cholecystectomy) has been evaluated compared to operative management in a single stage (Rendezvous). The latter seems to be more cost-effective. However, as noted in local studies, not all surgical teams have the necessary training and instruments to perform it. Most studies have limitations regarding model adaptation based on different insurance systems and resource availability. This limitation has implications for timely care and the need to refer patients to institutions with a higher level of care for diagnostic studies (especially NMRC and EUS) and definitive treatment. New studies still need to discuss these aspects to determine the indirect costs derived from applying the care models to contexts with limited resources.

Grounded on the limitations identified in the available literature regarding the cost-effectiveness of prediction models to diagnose and treat secondary cholelithiasis, the new studies may focus on evaluating:
The cost-effectiveness and economic impact of the models on health institutions and systems

Which model offers the best cost-effectiveness in different practice contexts

The adherence of professionals to models and its impact on cost-effectiveness

The clinical impact related to the long waiting times for non-invasive diagnostic tests and the need for referral, as well as the economic impact derived from these delays on the health system and the institution.

These objectives should be achieved on significant population samples that allow extrapolating the cost-effectiveness analysis on the diagnosis, preferably from national databases or insurance systems, which can go hand in hand with the viability of clinical trials as secondary analysis objectives.

CONCLUSION

The prediction of choledocholithiasis remains controversial. Multiple aspects have revolutionized risk determination, such as the refinement of endoscopic techniques for diagnostic and therapeutic purposes and the development of non-invasive diagnostic methods such as EUS and NMRC. Nevertheless, it is imperative to identify the knowledge gaps in the scientific literature to improve the available prediction models. It is still necessary to assess the variables included in the prediction models, such as relative weight and interaction. The available models must be externally validated in multiple contexts and populations. Likewise, studies on reducing the diagnostic uncertainty related to determining risk thresholds and their application to special groups are required. Finally, delving into the models’ economic impact on the health system and institutions is needed.

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