Effect of a Deep Learning-based Bile Duct Scanning System on the Diagnostic Accuracy of Common Bile Duct Stones During Examination by Novice Ultrasound Endoscopists: a Single-center, Tandem, Randomized Controlled Trial

Short Title：IREAD Study

NCT	
Trial number	EA-22-004
Protocol version	1.1
Version date	May 17, 2022
Country	China
Device	IREAD
Principal investigator	Professor HonggangYu
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Content

1. Summary

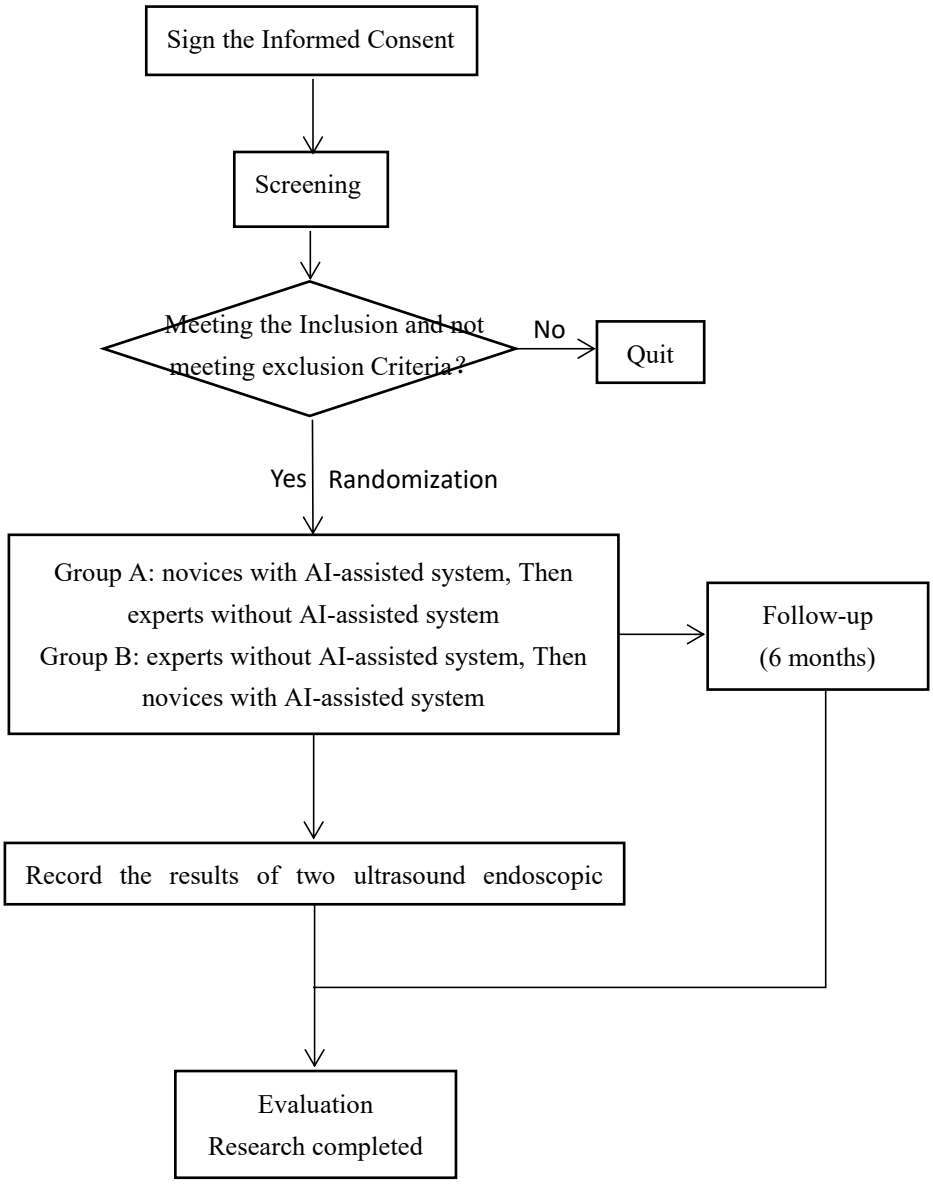
Title：	Effect of a Deep Learning-based Bile Duct Scanning System on the Diagnostic Accuracy of Common Bile Duct Stones During Examination by Novice Ultrasound Endoscopists: a Single-center, Tandem, Randomized Controlled Trial
Short Title：	*IREAD Study*
Trial number：	EA-22-004
Research system：	IREAD
Expected effect：	A single-center, tandem, randomized controlled trial was conducted to evaluate the effectiveness and safety of the proposed deep learning-based bile duct sweep system in improving the diagnostic accuracy of common bile duct stones and reducing the rate of missed gallstones during bile duct sweeps by novice ultrasound endoscopists.
Primary Endpoint：	Accuracy of diagnosis of common bile duct stones in patients with low and intermediate risk by novice combined with AI-assisted and expert
Secondary Endpoints:	1）Sensitivity, specificity, NPV, and PPV for the diagnosis of common bile duct stones in low and intermediate risk patients 2）Detection rate of gallstone lesions 3）Missed detection rate of gallstone lesions 4）Detection rate of bile duct lesions(all bile duct lesions including gallstones) 5）Missed rate of bile duct lesion(all bile duct lesions including gallstones) 6）Number of bile duct standard station scans 7）scan time 8）Incidence of Adverse Events
Trail design：	Single center, prospective, tandem, randomized control
Participants：	Male and female subjects aged 18 years and older at low to moderate risk of suspected common bile duct stones are required to undergo ultrasound endoscopy, voluntarily provide endoscopic imaging and sign an informed consent form
Sample size：	184 samples were collected to explore the sample distribution, and then calculate the sample size according to the sample distribution.

Study Process：	Determination of entry and exclusion criteria was performed before performing ultrasound endoscopy, and subjects who met all entry criteria and did not meet all exclusion criteria were included in the study. All patients who met the entry-exclusion criteria were randomized 1:1 into two groups A and B for a tandem, randomized controlled trial. Patients in group A were first swept by the novice endoscopist with the assistance of a deep learning-based bile duct sweep system during the examination, and then re-swept by the specialist without AI assistance after the sweep was completed; patients in group B were first swept by the specialist without AI assistance during the examination, and then swept by the novice endoscopist with AI assistance after the sweep was completed. Novice physicians and specialists were unaware of each other's sweeps, and subjects were unaware of their grouping. The recorder recorded the bile duct sweep results of the novice physicians and specialists during the 2 examinations in real time, and the patients were still to be followed up for 6 months after the procedure (telephone follow-up in months 1, 2, 3, and 6 with instructions to review liver function and abdominal ultrasound), and the end of the follow-up was the end of the study; the results of the collected patient examinations were transmitted to an independent data analysis group for review, and the review group was unaware of the subgroup of subjects.
Security：	Safety incidents shall be evaluated and reported according to the quality management measures for clinical trials of medical devices

1.1 Time and Event Tables

Events	Screening period （ d -30~0）	The day of Ultrasound Endoscopy（d 0）	Follow up (（d 0~180）
Informed Consent	X		
Basic characteristics	X		
Medical history/surgical history	X		
Physical Examination	X		
Inclusion/Exclusion Criteria		X	
Ultrasound Endoscopy		X	
Concomitant treatment	X	X	
Concomitant medication	X	X	
Adverse Events		X	X
Follow-up results (6 months)			X
Research completed			X

1.2 Flow chat



2. Introduction

The incidence of gallstones has been increasing in recent years, up to 10-15% in developed countries, and is still increasing at a rate of 0.6% per year. It is estimated that common bile duct stones (CBDS) are present in about 10-20% of patients with symptomatic bile duct stones. Each year, common bile duct stones lead to acute complications such as biliary obstruction, cholangitis and acute pancreatitis in a large number of patients, seriously endangering their lives and health. In addition, Diagnostic Related Group (DRG) analysis shows that each episode of common bile duct stone costs $9,000, and acute pancreatitis that progresses from common bile duct stones can result in 275,000 hospitalizations and $2.6 billion in costs each year, imposing a significant

economic and health burden on society. Therefore, timely diagnosis of common bile duct stones and intervention for them are crucial. Endoscopic retrograde cholangiopancreatography (ERCP) is the method of choice for the diagnosis and treatment of CBDS, and guidelines recommend stone extraction for all patients with CBDS who are physically fit enough to tolerate ERCP operations. However, ERCP is a highly demanding and risky operation with the potential for serious complications such as PEP (incidence 2.6-3.5%). How to diagnose choledocholithiasis early and accurately, achieve timely patient intervention to improve prognosis, and avoid unnecessary medical operations to reduce risks are our current challenges to be solved.

The European Society for Gastrointestinal Endoscopy (ESGE) and the American Society for Gastrointestinal Endoscopy (ASGE) recently updated their guidelines for the endoscopic management of patients with suspected common bile duct stones, providing risk stratification for more accurate management in the evaluation and treatment of suspected CBDS. Based on ESGE risk stratification criteria, patients with features of cholangitis or common bile duct stones on abdominal ultrasound are classified as high risk, patients with abnormal liver function tests (LFTs) and/or abdominal ultrasound showing CBD dilatation are classified as intermediate risk, and patients with normal liver function tests and abdominal ultrasound are classified as low risk. It is recommended that patients in the intermediate risk group for CBDS and in the low risk group for whom the physician still has a high suspicion of CBDS be recommended to undergo ultrasound endoscopy (EUS) or magnetic resonance cholangiopancreatography (MRCP) to determine the presence of CBDS, depending on the local level of care. . In addition, a cost-effectiveness analysis showed that MRCP would be the preferred test when the predicted probability of CBDS is less than 40%, while EUS is the preferred test when the predicted probability is 40%-90%. Compared to MRCP, EUS is widely available but has a steep learning curve. the ASGE guidelines state that a minimum of 225 EUS operations are required to qualify, while ESGE states that a minimum of 300 operations are required. However, this experience can only be gained at training centers that perform a large number of cases. Thus, the training of novice physicians in resource-limited areas is a huge challenge, which leaves a significant shortage of experienced ultrasound endoscopists and poor performance in the actual diagnosis of common bile duct stones, greatly limiting the popularity of ultrasound endoscopy.

AI technology has developed rapidly in the medical field in recent years, and several studies have shown that the diagnostic capability of AI has surpassed that of human experts in certain diseases, and there are also related studies that confirm the feasibility of AI application in ultrasound endoscopic image recognition. In our previous research, using AI technology to assist ultrasound endoscopists in film reading can significantly improve the accuracy of ultrasound image localization and anatomical marker segmentation by physicians, and we successfully built a deep learning-based bile duct segmentation and site identification system. Based on this, we develop a deep learning-based bile duct sweep system to assist novice ultrasound endoscopists in performing bile duct sweeps to identify common bile duct stones. The AI-based technology allows novice ultrasound endoscopists to obtain diagnostic quality equivalent to that of experts with minimal training, which helps to detect choledochal stones in a timely manner and improve their diagnostic accuracy for choledochal stones, alleviating the current shortage of experienced endoscopists and enabling early diagnosis and precise treatment of patients.

3. Patient Selection

The subject population of ultrasound endoscopy patients in this study was male and female subjects aged 18 years (and older) at low to intermediate risk of suspected common bile duct stones who were required to undergo ultrasound endoscopy, voluntarily provided endoscopic imaging and signed an informed consent form, and such patients were enrolled in the study.

Patients not meeting the inclusion criteria or meeting exclusion criteria will not be considered for participation in the study. Patients who met all criteria and singed informed consent may be excluded from the study due to:

• Endoscopists' professional advices/medical reasons (only under very limited conditions to avoid researcher bias).

• Withdraw informed consent.

Novice ultrasound endoscopists in this study were defined as endoscopists with 3 or more years of gastrointestinal experience and less than 25 cases of independent ultrasound endoscopy; experts were defined as endoscopists with at least 3 years of ultrasound endoscopy experience.

3.1. Inclusion criteria

All patients meeting the following criteria will be considered for participation in the study:

1) Males and females aged 18 years and older who are suspected of having common bile duct stones at intermediate to low risk, where intermediate-risk patients are those with normal liver function but with abdominal ultrasound suggestive of bile duct dilatation, and low-risk patients are those with normal abdominal ultrasound and liver function but whose physicians still suspect common bile duct stones;
2) Able to read, understand and sign an informed consent;
3) The investigator believes that the subjects can understand the process of the clinical study, are willing and able to complete all study procedures and follow-up visits, and cooperate with the study procedures.

3.2. Exclusion criteria

All patients meeting the following criteria will not be considered for participation in the study:

1) Patients at high risk of common bile duct stones. High-risk patients are those with common bile duct stones detected by abdominal ultrasound, patients with manifestations of cholangitis or hospitalized patients with a history of gallbladder stones with pain, bile duct dilatation and jaundice;
2) Have drug or alcohol abuse or mental disorder in the last 5 years;
3) Pregnant or lactating women;
4) Altered anatomy due to previous history of upper gastrointestinal surgery;
5) Patients with advanced tumors resulting in abnormal upper gastrointestinal anatomy;

6) High-risk diseases or other special conditions that the investigator considers the subject unsuitable for participation in the clinical trial.

3.3. Definition of enrollment

After participants signed informed consent, they were regarded as enrolled. The sign time was the enrollment time, and was recorded in CRF.

4. Endpoints

4.1. Primary Endpoint

Accuracy of novice combined with AI-assisted and expert in the diagnosis of common bile duct stones in low to intermediate risk patients: ERCP and 6-month follow-up results as gold standard. A true positive was defined as CBD stones detected by EUS and the presence of CBD stones confirmed at ERCP; a false positive was defined as CBD stones detected by EUS and the absence of CBD stones confirmed by ERCP; a true negative was defined as CBD stones not detected by EUS and as CBD stones detected at 6-month follow-up; a false negative was defined as CBD stones not detected by EUS and subsequent ERCP or CBD stones were detected at 6-month follow-up.

4.2. Secondary Endpoints

1) Sensitivity, specificity, NPV, and PPV for the diagnosis of common bile duct stones in low and intermediate risk patients
2) Detection rate of gallstone lesions
3) Missed detection rate of gallstone lesions
4) Detection rate of bile duct lesions(all bile duct lesions including gallstones)
5) Missed rate of bile duct lesion(all bile duct lesions including gallstones)
6) Number of bile duct standard station scans
7) Scan time

Incidence of Adverse Events

4.3. Safety evaluation endpoints and other secondary endpoints

Adverse events shall be determined according to the definition in the code for the quality management of adverse events of medical devices.The following types of adverse events should be recorded and calculated in the hospital history and CRF. According to the CRF table, the

occurrence time, starting and ending time, intervention measures and treatment results should be filled in when recording. The severity should be referred to the previous literature and CTCAE 5.0 standard.

5. Purpose and overall design

5.1. Purpose

The purpose of this study was to evaluate the effectiveness and safety of the proposed deep learning-based bile duct sweep system in improving the diagnostic accuracy of common bile duct stones and reducing the rate of missed gallstones during bile duct sweeps by novice ultrasound endoscopists through a single-center, tandem, randomized controlled trial.

5.2. Overall design

This study is a prospective, single-center, tandem, randomized controlled clinical study. The study was conducted at the Renmin Hospital of Wuhan University, and the number of included samples was decided according to the specific experimental protocol, and 184 subjects were expected to be included.

6. Study process

6.1. Summary of Study Process

• If the patient meets the inclusion criteria, the patient is invited to participate in the study and then the informed consent procedure for the clinical trial is applied.
• Assess patients' eligibility based on the inclusion/exclusion criteria.
• If the patient meets the inclusion/exclusion criteria, information prior to endoscopy will be collected.
• A colonoscopy is performed after informed consent. Any intraoperative adverse events are recorded on the CRF for submission and subsequent analysis.
• Follow-up will be performed from the postoperative to the study completion, as detailed in the time and event table.

6.2. Enrollment

Only after patients signed the informed consent, can the research-related procedures be conducted.

6.2.1. Informed Consent

According to the Helsinki Declaration, patients are not allowed to participate in the study without adequate informed consent. The principal investigator is responsible for ensuring that no patient was enrolled in the study without adequate informed consent. Failure to obtain informed consent and failure to document this process is considered a violation of the Helsinki Declaration and the study protocol.

All informed consent documents (ICDs) must be approved by ethics. Patient's informed consent requires documentary record on the informed consent by himself in his primary language.

The investigator or trained designated person performs a preliminary screening to determine if the patient generally meets the eligibility criteria for the study. If yes, the investigator or trained designee should recommend the patient to participate in the study. If the patient agrees to participate, they will need to sign an informed consent document.

The investigator or trained designated person should confirm that the subject understands the following points in the study:

• the purpose of research,
• potential risks or adverse events,
• Potential risks or adverse events directly related to participating the research,
• The likelihood of failure,
• Research requirements include follow-up visits,
• All rights of the subject as a participant in the clinical study.

After explaining the purpose of the study, the investigator or trained designee should answer any questions from the subject. If the subject agrees to participate, his or her wishes must be recorded by signing and dated on the EC-approved ICF, and the document should be signed and dated by the patient receiving the informed consent.

After successful completion of the informed consent process, the investigator or trained designated person will assess the eligibility of patients based on the protocol.

6.2.2. Patient Selection

All patients who underwent Ultrasound Endoscopy, agreed to use artificial intelligence and generally meet the study requirements were screened based on the inclusion/exclusion criteria. Patients who passed the screening were enrolled and recorded in the subject screening and enrollment tables. There is no bias in the choice of the enrolled subjects. The date of screening, the results (enrolled or not), and the primary reason for not selecting subjects (such as not meeting inclusion criteria, or not interested in participating in the study) will be recorded.

After the patients are enrolled, the research center should complete the preoperative study data collection.

It is desirable to be able to collect complete data for all enrolled patients, without those withdrawal from the study。

6.2.3. Subject identification number

Patients were numbered after signing informed consent.

The subject number begins with EA as a fixed number and is numbered starting from 0001 at the time of signing the informed consent. For example, the first patient who signed the informed consent was EA0001, and the second one was EA0002.

Once the subject identification number is assigned, the number is not reusable.

6.3. Treatment Description

This section applies to individuals who have signed an approved informed consent and have been identified as eligible to participate in this study on the basis of the inclusion and exclusion criteria. This section introduces the preoperative, surgical and postoperative management of subjects in detail.

6.3.1. Patient Screening Assessments

1） History
2） Physical examination
3） Hematuria pregnancy test (if required)

6.3.2. Pre-Procedure Managements

1） Routine condition assessment.
2） Psychological counseling.
3） Perform routine patient anesthesia.

6.3.3. Intraoperative Managements

1） Subject position: lateral recumbent position with appropriate restraint.
2） Insertion route: chosen according to the subject's actual condition, usually transoral.
3） Bile duct sweep with novice followed by expert or expert followed by novice depending on the grouping.
4） Intraoperative abnormal findings must be scrutinized through standard clinical procedures, and photographs must be kept for documentation of any findings during ultrasound endoscopy.

6.3.4. Post-operative Managements

1） Routine postoperative care.
2） Subjects were observed until awakening.

3） Those without choledochal stones detected were followed up for 6 months (1st, 2nd, 3rd, and 6th months by telephone and instructed to review liver function and abdominal ultrasound).
4） Examination information, such as subject grouping, examining physician, examination time, sedation status, number of common bile duct stones found, and number of bile duct site scans, was recorded by the recorder.
5） Images, videos, and case data of the examination were collected.

6.4. Suspension and withdrawal

Patients who were screened and confirmed to be eligible for the study, signed the informed consent and completed the randomization were considered as enrolled. If serious program deviation, withdrawal, or death occurs, the subject study is considered to be suspended. If the subject discontinues the study after obtaining informed consent, the data before the discontinuation will still be included in the study-related analysis.

6.4.1. Pre-Procedure

In any time during the study period, even before colonoscopy, participants could withdraw their informed consent whenever necessary. Researchers can withdraw participants before surgery according to safety considerations in the inclusion and exclusion criteria.

6.4.2. Intraprocedure

For safety reasons, the investigator may have the subject quit during the procedure. For example, the patient is not suitable for receiving the instrument for the study or the endoscopists do not use the specified instrument for any reason. If the following serious cases occur, please withdraw during the operation:
1） Perforation
2） Bleeding
3） Allergy to narcotic drugs
4） The anatomical structure of the upper gastrointestinal tract is abnormal and the endoscopist cannot enter the scope smoothly
5） Inability to complete ultrasound endoscopy due to obstruction, intolerance, etc.
6） Unable to complete colonoscopy due to obstruction or other reasons

6.4.3. Replacement

Subject will be deemed to have commenced the study upon completion of the informed consent process, and any subject who has been discontinued prior to or during the endoscopic examination will not subsequently be replaced by other subjects.

6.5. Blindness and Uncovering Blindness

The study was blinded to the subjects, who were unaware of their grouping, and to the data review panel, whose members were unaware of the subjects' grouping.

Unblinding or blinding-breaking, i.e., presenting randomization results to subjects or evaluators, should be protected by the investigator whenever possible. Unblinding of randomization results for a single subject may lead to the disclosure of randomization results for other subjects, and any disclosure of randomization results can have a significant impact on the statistical analysis. Approach blinding disclosures with caution in general, and consider unblinding in the following circumstances：

1) Endangering the safety of the subject: For example, in some serious adverse events, the subject needs to know the randomization results to inform other physicians to take appropriate emergency treatment.

2) Endangering assessor safety: When the assessor faces a safety hazard and needs to know the randomization results.

3) Study compliance: For partial compliance reasons, disclosure of randomization results to the appropriate authorities or the public is required in specific circumstances, such as for unanticipated adverse events that require disclosure of the study system and the cases in which it is involved.

4) Other regulatory reasons.

7. Basis of study protocol and risk/benefit analysis

The use of a deep learning-based bile duct scanning system provides information to novice endoscopic ultrasound practitioners on the diagnosis and treatment of common bile duct stones, which does not provide a final diagnosis, the novice doctors make their own diagnosis and follow-up diagnosis and treatment on the basis of the tips from the bile duct site identification and common bile duct stones, in the end, the results of endoscopic sonography were compared with those of novices and experts, and the results of experts were taken into account when they were inconsistent.

7.1. Selection of endpoints

The primary evaluation endpoint was the accuracy of the diagnosis of common bile duct stones in low- and intermediate-risk patients by the novice combined with AI-assisted and expert.

The secondary endpoints were sensitivity, specificity, NPV, and PPV of common bile duct stone diagnosis in low- and intermediate-risk patients; bile duct EUS sweep gallstone lesion detection rate; bile duct EUS sweep gallstone lesion miss rate; bile duct EUS sweep lesion detection rate (all bile duct lesions including gallstones); bile duct EUS sweep lesion miss rate (all bile duct lesions including gallstones); bile duct site Number of sweeps; sweep time; adverse event rate.

Adverse events in safety indicators shall be judged in accordance with relevant regulations, and serious adverse events shall be recorded and reported in accordance with regulations.

7.2. Definition of participants

Patients were included according to the indications and contraindications described in the use plan. Because of practical reasons (such as younger patients, participation in a number of clinical studies, alcohol/drug dependence patients, and other factors that may affect the completion and/or reliability of Ultrasound Endoscopy) and ethical reasons (whether informed consent can be completed, etc.), the entry and discharge criteria have been reduced.

7.3. Adverse events

The relevant definitions of adverse events are as follows:

Adverse Events (AE): Any adverse medical event, unexpected disease or injury, or adverse clinical manifestations (including abnormal laboratory findings) that occur in a subject, user or other person, whether or not associated with medical devices.

Serious Adverse Events (SAE): Adverse Events with the following information:

- causing death.
- leading to severe deterioration of the health of the subjects, including
- leading to life-threatening diseases or injuries,
- Causing impairment of body structure or function.
- Need hospitalization or extended hospitalization
- lead to hospitalization and preventive medical or surgical intervention
- Permanent damage to body structure or function
- Fetal distress, fetal death or congenital abnormalities or congenital defects.

Note: Hospitalization for existing conditions, or surgery required in the program, without serious deterioration of health status, is not considered a serious adverse event. Purposeful hospitalization, such as economic or reimbursement reasons, is not considered a serious adverse event.

Unexpected adverse device response (UADE): refers to adverse events related to medical devices that were not previously identified in the current version of the risk analysis report in terms of nature, severity or incidence. The definition includes any event caused by insufficient or inadequate description of the use or deployment of the device. This definition includes any event caused by a user's error.

7.4. Expected and trial-related adverse events

Previous studies have shown that the expected adverse events are basically the same as the complications of conventional endoscopic diagnosis and treatment.

The instrument used in this experiment is a medical software which is not in contact with

human body. There is no difference between the experimental operation and the routine operation. The intervention measures (such as randomized process) in the experiment may slightly increase the incidents of diagnosis and treatment.

7.5. Risk minimization

In this study, when the software malfunctioned, novice doctors and experts could still operate under their own judgment without affecting the routine treatment measures, and when the judgment of the two did not agree, the expert results prevailed, which greatly reduced the risk of the trial.

7.6. Related benifits

In this study, novice endoscopists were assisted by a deep learning-based bile duct sweep system to identify common bile duct stones. The AI-based technology allows novice ultrasound endoscopists to obtain diagnostic quality equivalent to that of experts with minimal training, helping to detect common bile duct stones in a timely manner and improve their diagnostic accuracy for common bile duct stones, alleviating the current shortage of experienced endoscopists and enabling early diagnosis and precise treatment of patients.

7.7. Overall feasibility analysis

The deep learning-based bile duct scanning system is an independent system including both software and computer hardware, which can monitor image data 24 hours a day. The system is not invasive. The overall operability is strong.

8. Statistical Analysis

8.1. Statistical Analysis Plan

Data management and statistical analysis were implemented by Renmin Hospital Wuhan University.

8.2. Methods

1）Means and standard deviations for continuous variables with equal distribution and medians for non-equal distribution; percentages for categorical variables.
2）Continuous variables were compared by t-test (e.g., age) or Mann-Whitney U test (bilirubin, aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase).
3）Categorical variables were compared using McNemar's test.

8.3. Sample Size Calculation

For the sample size determination, the level of bilateral significance was 5% (α=5%),80% certainty (β=20%), and based on previous reports of 90% diagnostic accuracy of endoscopists for common bile duct stones, a non-inferiority test of novice combined with AI non-inferiority to expert was performed, and a total of 147 patients were calculated to be enrolled. Assuming a 20% shedding rate, a total of 184 subjects were expected to be enrolled.

8.4. Statistical analysis set

All patients who met the inclusion and exclusion criteria were considered eligible for recruitment.

The two analysis sets in this study are defined as follows:

• The full analysis set (FAS) population analysis set will contain all eligible cases and shedding cases, but does not include culling cases.

• The Compliance (PP) population analysis set will include all subjects in the FAS analysis set with no significant deviation from the program.

Intention-to-treat and conformity analysis sets should be used to analyze the primary efficacy endpoints. The main analysis will be based on the PP analysis set. FAS analysis was regarded as supportive analysis.

9. Abbreviations

Abbreviations	Full Name	Chinese
AE	Adverse Event	不良事件
CFDA	China Food and Drug Administration	国家食品药品监督管理总局
CNDA	China National Drug Administration	国家食品药品监督管理总局
CRF	Clinical Record File	病例报告表
EUS	Ultrasound Endoscopy	超声内镜
CTCAE	Common Terminology Criteria for Adverse Events	不良事件常规评价标准
EC	Ethical Committee	伦理委员会
HBV	Hepatitis B Virus	乙型肝炎
ICD	Informed Consent Document	知情同意文件
ICF	Informed Consent Form	知情同意书
ITT	Intention To Treat	意向治疗分析集
PP	Per Protocol	符合方案集
SAE	Serious Adverse Event	严重不良事件

Informed Consent Form

"Effect of a Deep Learning-based Bile Duct Scanning System on the Diagnostic Accuracy of Common Bile Duct Stones During Examination by Novice Ultrasound Endoscopists: a Single-center, Tandem, Randomized Controlled Trial"

Informed Consent Form for clinical study subjects

Informed Consent Form:Information page

Release date: 1.0,13 May 2022
Principal investigator: Yu Honggang
Dear sir / Madam,

We will invite you to participate in a clinical study "Effect of a Deep Learning-based Bile Duct Scanning System on the Diagnostic Accuracy of Common Bile Duct Stones During Examination by Novice Ultrasound Endoscopists: a Single-center, Tandem, Randomized Controlled Trial". During this study, we will collect your colonoscopy video for analysis by a new colonoscopy-assisted system to derive your score of bowel preparation, Doesn't interfere the physician's original observations and procedures.

Before you decide whether to participate in the study, please read the following as carefully as possible to help you understand the study and why it was conducted, the procedure and duration of the study, the potential benefits or risks of participating in the study. If you wish, you can discuss it with your family or friends, or ask your doctor for an explanation to help you make a decision.

1.Background and Purpose

The incidence of gallstones has been increasing in recent years, up to 10-15% in developed countries, and is still increasing at a rate of 0.6% per year. It is estimated that common bile duct stones (CBDS) are present in about 10-20% of patients with symptomatic bile duct stones. Each year, common bile duct stones lead to acute complications such as biliary obstruction, cholangitis and acute pancreatitis in a large number of patients, seriously endangering their lives and health. In addition, Diagnostic Related Group (DRG) analysis shows that each episode of common bile duct stone costs $9,000, and acute pancreatitis that progresses from common bile duct stones can result in 275,000 hospitalizations and $2.6 billion in costs each year, imposing a significant economic and health burden on society. Therefore, timely diagnosis of common bile duct stones and intervention for them are

crucial. Endoscopic retrograde cholangiopancreatography (ERCP) is the method of choice for the diagnosis and treatment of CBDS, and guidelines recommend stone extraction for all patients with CBDS who are physically fit enough to tolerate ERCP operations. However, ERCP is a highly demanding and risky operation with the potential for serious complications such as PEP (incidence 2.6-3.5%). How to diagnose choledocholithiasis early and accurately, achieve timely patient intervention to improve prognosis, and avoid unnecessary medical operations to reduce risks are our current challenges to be solved.

The European Society of Gastrointestinal Endoscopy (ESGE) and the American Society of Gastrointestinal Endoscopy (ASGE) have recently updated their guidelines for the endoscopic management of patients with suspected common bile duct stones, recommending that ultrasound endoscopy (EUS) or magnetic resonance cholangiopancreatography (MRCP) be recommended for patients in the intermediate risk group for CBDS and in the low risk group where the physician still has a high suspicion of CBDS, depending on the local level of care, to determine the presence of CBDS. Studies have shown that the diagnostic performance of EUS and MRCP is comparable, but EUS is more sensitive than MRCP for small stones less than 6 mm. In addition, a cost-effectiveness analysis showed that MRCP would be the preferred test when the predicted probability of CBDS is less than 40%, while EUS is the preferred test when the predicted probability is 40%-90%. Compared to MRCP, EUS is widely available but has a steep learning curve. the ASGE guidelines state that a minimum of 225 EUS operations are required to qualify, while ESGE states that a minimum of 300 operations are required. However, this experience can only be gained at training centers that perform a large number of cases. Thus, the training of novice physicians in resource-limited areas is a huge challenge, which leaves a significant shortage of experienced ultrasound endoscopists and poor performance in the actual diagnosis of common bile duct stones, greatly limiting the popularity of ultrasound endoscopy.

AI technology has developed rapidly in the medical field in recent years, and several studies have shown that the diagnostic capability of AI has surpassed that of human experts in certain diseases, and there are also related studies that confirm the feasibility of AI application in ultrasound endoscopic image recognition. In our previous research, using AI technology to assist ultrasound endoscopists in film reading can significantly improve the accuracy of ultrasound image localization and anatomical marker segmentation by physicians, and we successfully built a deep learning-based bile duct segmentation and site identification system. Based on this, we develop a deep learning-based bile duct sweep system to assist novice ultrasound endoscopists in performing bile duct sweeps to identify common bile duct stones. The AI-based technology allows novice ultrasound endoscopists to obtain diagnostic quality equivalent to that of experts with minimal training, which helps to detect choledochal stones in a timely manner and improve their diagnostic accuracy for choledochal stones, alleviating the shortage of experienced endoscopists and enabling early diagnosis and accurate treatment of patients. To this end, we built IREAD, a bile duct scanning system based on deep learning, to assist novice physicians in bile duct scanning and common bile duct stone detection, and validated the effectiveness and safety of the AI-assisted system to improve the diagnostic accuracy of common bile duct stones under ultrasound endoscopy through a single-center, tandem, randomized controlled study.

2.Who can participate in the study

1) Males and females aged 18 years and older who are suspected of having common bile duct stones at intermediate to low risk, where intermediate-risk patients are those with normal liver function but with

abdominal ultrasound suggestive of bile duct dilatation, and low-risk patients are those with normal abdominal ultrasound and liver function but whose physicians still suspect common bile duct stones;
2) Able to read, understand and sign an informed consent;
3) The investigator believes that the subjects can understand the process of the clinical study, are willing and able to complete all study procedures and follow-up visits, and cooperate with the study procedures.

3.Who can not participate in the study

1) Patients at high risk of common bile duct stones. High-risk patients are those with common bile duct stones detected by abdominal ultrasound, patients with manifestations of cholangitis or hospitalized patients with a history of gallbladder stones with pain, bile duct dilatation and jaundice;
2) Have drug or alcohol abuse or mental disorder in the last 5 years;
3) Pregnant or lactating women;
4) Altered anatomy due to previous history of upper gastrointestinal surgery;
5) Patients with advanced tumors resulting in abnormal upper gastrointestinal anatomy;
6) High-risk diseases or other special conditions that the investigator considers the subject unsuitable for participation in the clinical trial.

4.What would you need to do

Patients need to prepare routinely for the ultrasound endoscopy operation by fasting for at least 8 hours and 2 hours before the operation; receive routine anesthesia; and you will be randomly assigned to be scanned by a novice endoscopist with the assistance of the bile duct scanning system, followed by a specialist endoscopist; or scanned by a specialist endoscopist, followed by a novice endoscopist with the assistance of artificial intelligence. The bile duct scanning system provides real-time alerts to the novice endoscopist about the current scanning site and the presence of common bile duct stones. You are equally likely to be placed in either of these groups.

5.Benefits

Your ultrasound endoscopic image data can be automatically evaluated by the artificial intelligence bile duct scanning system free of charge. The bile duct scanning system can assist novice ultrasound endoscopists in scanning standard bile duct sites and detecting common bile duct stone lesions, reducing the dependence of the examination on the endoscopist's clinical experience and subjective state, improving the quality of the examination and the accuracy of the diagnosis of common bile duct stones.

6.Adverse events

The adverse events are basically the same as the complications of conventional Ultrasound Endoscopy diagnosis and treatment.Participation in this study does not increase other additional risks.

7.Related fees

Routine ultrasound endoscopy is a clinical examination at your own expense. You will only be responsible for the cost of one ultrasound endoscopy, and there will be no increase in the cost of your treatment.

8.Personal Information

During the colonoscopy process, your endoscopic electronic images and case information will be collected and preserved in the hospital. Your doctor, the researcher, will be given access to this electronic information for scientific research. Your personal identity will not be disclosed in any public report of the results of the relevant research and development. We will do everything within the law to protect the privacy of your personal medical data.

9.For more information

You can ask any question about this study at any time.

Your doctor will give you his or her phone number so that he or she can answer your questions.

Your doctor will keep you informed if there is any important new information during the course of the study that may affect your willingness to continue participating in the study.

10.Participation and withdrawal are voluntary

Participation in the study is entirely up to you. You may refuse to participate in the study or withdraw from the study at any time during the course of the study. You will not be discriminated against or retaliated against for refusing to participate in the study. Your medical treatment and entitlements will not be affected.

Your doctor or researcher may suspend your participation at any time in the best interest of you.

If you withdraw from the study for any reason, you may also be required to undergo a laboratory and physical examination if your doctor deems it necessary.

If you choose to participate in this study, we hope that you can adhere to the completion of the entire research process.

11.Others

Participation in this study is up to you. You can discuss it with your family or friends before making a decision. Before you decide to participate in the study, ask your doctor as many questions as you can about the study until you have a complete understanding of it. Thank you for reading this. If you decide to participate in the study, please tell your doctor, he or she will arrange for you to participate in all matters related to the study. Please keep this information.

Informed Consent Form:Information page

Name of Clinical Research Project： Effect of a Deep Learning-based Bile Duct Scanning System on the Diagnostic Accuracy of Common Bile Duct Stones During Examination by Novice Ultrasound Endoscopists: a Single-center, Tandem, Randomized Controlled Trial

Research physician commitment:

As a research physician, I confirmed that I had clearly explained to the subject the details of this trial, including their rights and possible benefits and risks, and gave them a signed copy of my informed consent.

Name：_____ Date:_____

Contact：_____

Subject commitment:

I have read and understood the introduction to this study on the informed consent page, and have had the opportunity to ask questions. I understand the research physician's explanation.

I am aware of the risks and benefits of participating in this study. I am aware that participation in the study is voluntary, and I am sure that there has sufficient time to consider and volunteer for the trial. I can always ask my doctor for more information, and I can always withdraw from the study without discrimination or retaliation, and without prejudice to medical benefits and entitlements.

I also knew that if I dropped out of the study, I would tell my doctor and complete the physical and chemical tests. If I need to take any other medication for my illness, I will consult with my doctor in advance or tell him the truth afterwards.

I agree☐ or refuse☐ Use my medical records for any other study.

I agree to participate in the study and promised to follow the doctor's advice to the best of my ability. I will receive a signed and dated copy of the Informed Consent Form.

Name：_____ Date:_____

Contact：_____

-End-