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Detection of Undiagnosed Liver Cirrhosis via Artificial Intelligence-Enabled Electrocardiogram (DULCE): Rationale and design of a pragmatic cluster randomized clinical trial

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ABSTRACT

Background: Cirrhosis is a leading cause of morbidity and mortality worldwide, yet preventable at early stages. Currently, effective approaches for early diagnosis are lacking. A novel electrocardiogram (ECG)-enabled deep learning model trained for detection of advanced chronic liver disease (CLD) has demonstrated promising results and it may be used for screening of advanced CLD in primary care.

Design: A pragmatic, cluster randomized trial (**NCT05782283**) in 45 Mayo Clinic primary care practices will be conducted over a period of 6 months with 6 months of follow up. Care teams will be randomized 1:1 to intervention or usual care, stratified by region and patient volume. Patients from providers enrolled in the trial who undergo an ECG during the study period will be included. In the intervention arm, consenting providers to patients identified as higher risk of advanced CLD based on their ECG will be notified with a recommendation for noninvasive fibrosis assessment. The primary endpoint will be detection of advanced CLD (defined as stage 3–4 on blood- or imaging-based noninvasive liver disease assessment or liver biopsy). Secondary outcomes will include completion of fibrosis assessment tests within 180 days of ECG, new diagnosis of liver disease stratified by etiology and risk factors for CLD, and detection of any liver fibrosis (stages 1–4). Post-study surveys to participating clinicians will be conducted.

Summary: Preliminary findings suggest outstanding potential for the use of an ECG-enabled machine learning algorithm for detection of advanced CLD in the primary care community.

1. Introduction

Cirrhosis develops over many years of liver injury and often it remains asymptomatic until late stages of disease. Complications of decompensated cirrhosis and portal hypertension may include ascites, variceal hemorrhage, and hepatic encephalopathy. Approximately 2–5 % of the general population have significant undetected advanced liver fibrosis. Cirrhosis is among the leading causes of death in the United States and results from a wide range of infectious, metabolic, hereditary, toxic and autoimmune conditions [1]. Currently available laboratory-based markers of advanced liver fibrosis only have modest performance in the general population [2–4]. Thus, an opportunity exists for early detection of cirrhosis during which effective preventative and/or therapeutic interventions can be implemented. For instance, treatment of chronic liver diseases such as viral hepatitis C or B, alcohol use disorder, metabolic syndrome, and others, may successfully delay or prevent the progression of cirrhosis to decompensated stages or the development of hepatocellular carcinoma. In addition, nonselective beta-blockers have been shown to significantly decrease the incidence of gastroesophageal variceal bleeding and development of ascites in patients with compensated cirrhosis and their use in this population is recommended by both national and international society guidelines

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[5–7]. Novel screening tools with greater accuracy are needed to allow for early diagnosis and in turn effective interventions.

Cirrhosis is associated with cardiovascular changes and abnormalities on the electrocardiogram (ECG). The use of a tool such as an ECG for detection of unsuspected cirrhosis is of significant clinical value. Through a deep learning approach, we have trained and internally validated a convoluted neural network using digitized 12-lead ECG of 12,930 patients with cirrhosis (based on radiographic findings and ICD-9/-10 codes) and 64,577 controls. The model demonstrated excellent performance with an AUC of 0.858 and a diagnostic odds ratio of 12.33 (95 % CI: 11.16–13.63) [8]. Thus, the application of this artificial intelligence tool to routine 12-lead ECG may potentially be used for screening of asymptomatic and unsuspected advanced chronic liver disease (CLD) in primary care settings.

2. Methods

2.1. Study design

The Detection of Undiagnosed Liver Cirrhosis via Artificial Intelligence-Enabled Electrocardiogram (DULCE) is a cluster randomized controlled trial that will be conducted at 45 primary care practices in Rochester, and rural surrounding communities in Southeast and Southwest Minnesota as well as in Wisconsin. Primary care clinicians, including physicians, nurse practitioners and physician assistants, who care for adult patients ($\geq$18 years) and have the ability to order ECG will be consented. Clinicians will be randomized at the care team or individual level (when not part of a care team), with each serving as a cluster. Among the internal medicine and family medicine care teams across Mayo Clinic's practice in Rochester and Mayo Clinic Health Systems, those part of pediatric care, acute care, nursing home care and resident care teams, will be excluded.

2.2. Study population

The study population will include patients without a known diagnosis of cirrhosis that receive a 12-lead ECG for any indication during the study period. There will be no contact from the trial study team with patients. All the patient-level data will be collected from the EHR. Informed consent will be obtained from the clinicians, not the patients. A patient's data will be included if they are $\geq$18 years old and receive an ECG for any indication during the 6-month trial period. Patients with known cirrhosis based on noninvasive fibrosis assessment tests, liver biopsy or complications of decompensated disease, or with a documented history of cirrhosis identified by clinical notes will be excluded. Patients will be excluded if they have denied use of their medical records for research purposes, as per State of Minnesota statutes. Only the first ECG date per unique patient will be included in the study. If a provider withdraws from the trial prior to completion of the 6-month period, the observations acquired under that provider until their withdrawal will be included in the study.

2.3. Randomization

Randomization is conducted at the care team level or individual level, when not part of a care team. Each care team serves as a randomized cluster. Care teams will be randomized to intervention or usual care. The randomization will be stratified by region (Rochester, Southeast Minnesota, Southwest Minnesota, Northwest Wisconsin, and Southwest Wisconsin), and patient volume (i.e., the number of potential trial-eligible patients within the 6 months prior to randomization). We will send clinicians in the care teams an initial recruitment email. The email will explain that participation is voluntary and the choice not to participate will not affect their employment at Mayo Clinic. We will send another three follow-up email reminders to clinicians who do not respond to the initial email. If members of a care team decline participation, the care team will still be eligible for randomization if their colleagues in the same team decide to participate. The clinicians who decline participation will not have access to the report nor be contacted by the investigative team.

2.4. Intervention

The intervention itself will be an electronic notification via email of a positive ECG result. The machine learning (ML) model will be run every Monday in batches and clinicians in the intervention group will be notified every Tuesday, on a weekly basis if they had any patients with an ECG with a positive result in the preceding week. If patients have multiple ECG within the period leading to the weekly notification, the provider will be given the list of dates and times of all ECG and their DULCE score result (provided at least one result is positive). When the ECG-ML result is positive, clinicians will receive a recommendation for fibrosis assessment tests in the appropriate clinical context, such as age>40, type 2 diabetes, obesity, hyperlipidemia, hypertension, or other risk factors for liver disease. The decision to order additional testing will be up to the discretion of the providers and consideration of clinical context will be encouraged. Due to lack of imaging-based noninvasive liver disease assessment in rural primary care practices, a blood-based FibroTest will be suggested, which is available at all sites. Urban practices may also have access to vibration-controlled transient elastography (VCTE), magnetic resonance elastography (MRE) or liver biopsy, and these are acceptable alternatives. If the provider has not ordered a FibroTest in the following week post-notification, they will be sent a survey where they can document a reason for choosing not to proceed with further testing or if alternative testing (i.e. VCTE, MRE or biopsy) were obtained. Clinicians who are not randomized to the intervention group will not receive any contact from the investigators or study team. Clinical data will be abstracted from the EMR for 6 months (180 days) after ECG completion.

2.5. Baseline measurements

Clinicians' information, e.g., age, sex, specialty (e.g., internal medicine and family medicine), type (e.g., physician and advanced practice provider), and years of practice, will be captured at the time of informed consent via a link to a Redcap survey. Two follow-up reminder emails will be sent if no response is received. Patient baseline characteristics will be abstracted from EMR (Table 1). There will be no contact with patients for data collection. Index date is defined as the date when the ECG screening result is available for a patient. The time prior to the

Table 1
Patient baseline characteristics.

Variable class	Variables
Socio-demographic	Age, Sex, Race, Ethnicity, Rural/Urban Status, Marital Status, Insurance, Area Deprivation Index (ADI), HOUSES Index, Education Level
Medical History	Hypertension†, Diabetes†, Obesity‡, MI†, Atrial Fibrillation†, Other arrhythmias†, Obstructive Sleep Apnea†, Viral hepatitis†, Alcohol-associated liver disease†, Metabolic dysfunction-associated steatotic liver disease†, Other chronic liver disease†, Chronic kidney disease†, Cancer†, Prior hepatology consult, Smoking status*, Alcohol use*, Prior liver imaging, Serum creatinine#, Serum sodium#, Albumin#, Prothrombin time/INR#, Total bilirubin#, AST#, ALT#, Platelet count#
Medication Use	ACEi, ARB, Beta blocker[a], Diuretics, Other antihypertensives, Antidiabetic medications, Statins[b], Anti-craving medications

† Identified by diagnosis codes.
‡ Defined as BMI$\geq$30 kg/m^2.
* Structured fields in Epic.
# Most recent measurements prior to ECG.
[a] Classified by cardio-selective and non-selective and dose.
[b] Classified by high, medium and low doses.

index date is defined as this patient's baseline period, which will be used to collect medical history data. Additionally, ECG details such as DULCE score and location (emergency department vs not) will be collected.

2.6. Outcomes

The outcome measures (Table 2) will be assessed using the EMR within 180 days after the ECG. The primary objective of the trial is to validate a machine learning model for early detection of cirrhosis-associated signals on digitized ECG and apply this newly developed neural network for primary care screening of advanced chronic liver disease.

We will also pull the data for patients cared by the participating clinicians in the months prior to the start of the trial. We will collect the outcome data, such as the use of noninvasive liver disease assessments, to examine if the intervention group and the control group have similar practice patterns before the introduction of the intervention. If any substantial imbalance is found (typically defined by standardized difference>0.10), the baseline practice patterns will be accounted for in the analysis.

2.7. Sample size

Based on a prior study conducted at the proposed sites, we estimate a total of 22,000 ECGs in unique patients will be completed during the study period (11,000 in each arm). This estimate was based on a previous trial completed at these clinical sites [9]. With an estimated prevalence of 2–5 % in the general population, we should be adequately powered for detection of 50 % difference in the diagnosis of advanced CLD in the intervention arm compared to usual care during the proposed study period. Using a chi-squared test for a two-sample proportion comparison, 2578 observations per arm would be necessary to provide 85 % power to detect a difference between a 2 % and 1 % event rate. A potential pitfall is that we may not observe a significant overall difference due to potential lower prevalence of undiagnosed cirrhosis in the community. However, due to a significantly higher prevalence of advanced liver disease in individuals with underlying risk factors (obesity, metabolic syndrome, high risk alcohol use), we anticipate successfully achieving our secondary outcomes after stratifying by risk factors and etiology.

Table 2
Patient outcomes.

Outcomes	Description
Clinical Outcomes	
Primary Outcome (clinical)	Diagnosis of advanced liver fibrosis[a] within 180 days of index ECG
Secondary Outcomes (clinical)	New diagnosis of liver disease stratified by etiology (metabolic dysfunction associated steatotic liver disease, alcohol-associated liver disease, hepatitis C, and others) and presence of risk factors for CLD[b], and detection of any liver fibrosis (stages 1–4),
Healthcare Process/Quality Measures	
Secondary Outcomes (Healthcare Process and Quality Measures) within 180 days of index ECG	Completion of noninvasive fibrosis assessment tests, initiation of prophylactic nonselective beta-blockers, according to published society guidelines.

[a] Defined as stage 3–4 on blood- or imaging-based noninvasive liver disease assessment or liver biopsy.

[b] Age>40, type 2 diabetes, BMI≥30, hypertension, dyslipidemia, alcohol use disorder, chronic viral hepatitis.

2.8. Statistical analysis

We will compare the intervention and control groups in terms of both provider and patient characteristics. We will also compare the practice patterns during the three months prior to the trial. Imbalance in baseline variables will be assessed using standardized differences. If any significant imbalance (standardized difference>0.10) is detected, a sensitivity analysis will be performed including the unbalanced characteristics in the regression models for outcomes.

Analysis of the primary outcome (new diagnosis of advanced CLD) will be conducted using a mixed-effects model with a logit link to test differences in the incidence between the study arms. Care team will be included as a random effect. An F-test of the study arm parameter (using Satterthwaite's degrees of freedom for linear mixed models) will be used to test the primary hypotheses at the 0.05 Type I error rate. The study arm effect will be summarized as an odds ratio with a 95 % confidence interval. The frequency and percentage of the primary outcome will be summarized by arm as well. Sensitivity analyses will be conducted by including imbalanced baseline characteristics in the model. Subgroup analyses will be performed by including subgroups of interest to the primary model with an interaction term between subgroup and treatment arm. Tests of the interaction effect will be used to assess the significance of different treatment effects by subgroup. A priori subgroups of interest will be those stratified by age, sex, race (white non-Hispanic vs others), region (Rochester, Southwest Minnesota, Southeast Minnesota, Northwest Wisconsin, and Southwest Wisconsin), ADI National Rank (by tertile), HOUSES Quartile level, smoking status, alcohol use, obesity, hypertension and diabetes.

Analyses of secondary endpoints will be conducted in a similar fashion as the primary outcome, using mixed-effects models with a random effect for care team. The link function will depend on the response variable type with logit for binary variables and gaussian for continuous measures. Continuous measures with extremely skewed distributions will be transformed as needed.

Exploratory analyses will be performed to assess ordering patterns for noninvasive fibrosis assessments (blood- or imaging-based) within patients in the intervention arm with a positive ECG result. At the provider level this will include patterns according to each item in the clinician baseline questionnaire, as well as the end-of-trial questionnaires. At the patient level, we will explore patient baseline characteristics, in particular age, sex and socioeconomic variables such as education and the ADI and HOUSES indices. Such analyses will identify items that are most strongly related to the likelihood to order additional testing for a positive ECG result, and thus help refine the tool and guide future implementation strategies. An additional exploratory analysis will assess the relationship between the DULCE results in both arms and the likelihood of the primary outcome.

3. Discussion

With the rising prevalence of chronic liver disease and its comorbidities, effective population screening approaches are urgently needed. Widely available blood-based noninvasive liver disease assessment (i.e. Fib4, APRI) have modest accuracy, whereas imaging-based tests are not routinely available in primary care practices, particularly in rural communities. Thus, the use of ubiquitous, noninvasive and inexpensive 12-lead ECG for detection of CLD is appealing. Prior studies have demonstrated the feasibility and acceptance of ECG-enabled AI algorithms for community-based screening of cardiovascular conditions, including atrial fibrillation and cardiac dysfunction [10–12]. This pragmatic RCT aims to answer whether an ECG-enabled deep learning algorithm leads to increased diagnosis of CLD in routine primary care practice. The qualitative assessment will also explore how to best facilitate human-AI interaction and refine the implementation strategies, and thus, maximize the potential of AI in improving care delivery and patient outcomes.

The pragmatic design of this trial will provide important insights into not only the performance of this novel AI algorithm in primary care settings but also the potential barriers to implementation of such a tool. To help us understand the reasons why additional testing is not obtained following a positive test in at-risk patients, clinicians will receive reminders with a survey option for documentation.

In summary, we will conduct a pragmatic cluster RCT to test a newly developed ECG-enabled deep learning tool for screening of advanced chronic liver disease in primary care.

CRediT authorship contribution statement

Amy Olofson: Writing – review & editing, Writing – original draft, Project administration. **Ryan Lennon:** Writing – review & editing, Formal analysis, Data curation. **Blake Kassmeyer:** Writing – review & editing, Formal analysis, Data curation. **Kan Liu:** Writing – review & editing, Software, Methodology. **Zacchi I. Attia:** Writing – review & editing. **David Rushlow:** Writing – review & editing. **Puru Rattan:** Writing – review & editing. **Joseph C. Ahn:** Writing – review & editing. **Paul A. Friedman:** Writing – review & editing. **Alina Allen:** Writing – review & editing. **Patrick S. Kamath:** Writing – review & editing. **Vijay H. Shah:** Writing – review & editing. **Peter A. Noseworthy:** Writing – review & editing. **Douglas A. Simonetto:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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