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Utility of an Artificial Intelligence Enabled Electrocardiogram for Risk Assessment in Liver Transplant Candidates

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Abstract

Background

Post-operative cardiac complications occur infrequently but contribute to mortality after liver transplantation (LT). Artificial intelligence-based algorithms based on electrocardiogram (AI-ECG) are attractive for use during pre-operative evaluation to screen for risk of post-operative cardiac complications, but their use for this purpose is unknown.

Aims

The aim of this study was to evaluate the performance of an AI-ECG algorithm in predicting cardiac factors such as asymptomatic left ventricular systolic dysfunction or potential for developing post-operative atrial fibrillation (AF) in cohorts of patients with end-stage liver disease either undergoing evaluation for transplant or receiving a liver transplant.

Methods

A retrospective study was performed in two consecutive adult cohorts of patients who were either evaluated for LT or underwent LT at a single center between 2017 and 2019. ECG were analyzed using an AI-ECG trained to recognize patterns from a standard 12-lead ECG which could identify the presence of left ventricular systolic dysfunction (LVEF < 50%) or subsequent atrial fibrillation.

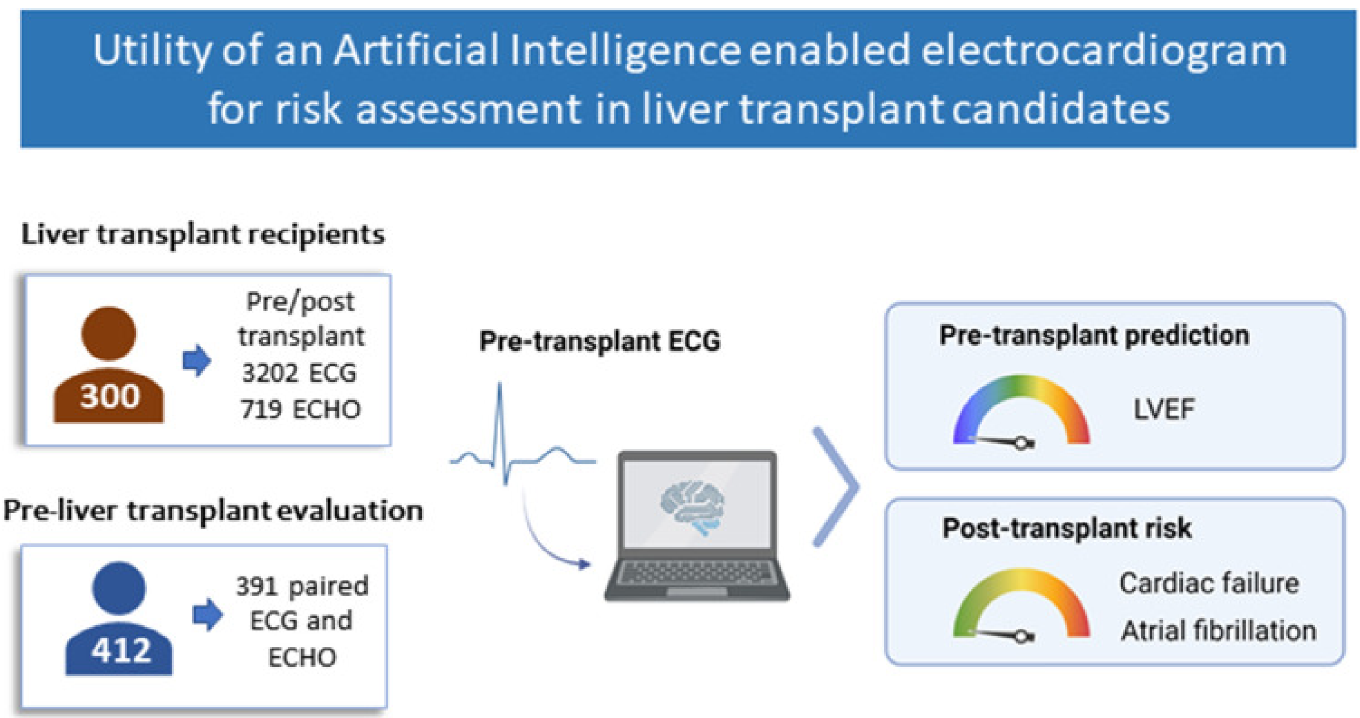
Results

The performance of AI-ECG in patients undergoing LT evaluation is similar to that in a general population but was lower in the presence of prolonged QTc. AI-ECG analysis on ECG in sinus rhythm had an AUROC of 0.69 for prediction of de novo post-transplant AF. Although post-transplant cardiac dysfunction occurred in only 2.3% of patients in the study cohorts, AI-ECG had an AUROC of 0.69 for prediction of subsequent low left ventricular ejection fraction.

Conclusions

A positive screen for low EF or AF on AI-ECG can alert to risk of post-operative cardiac dysfunction or predict new onset atrial fibrillation after LT. The use of an AI-ECG can be a useful adjunct in persons undergoing transplant evaluation that can be readily implemented in clinical practice.

Graphical Abstract



Supplementary Information

The online version contains supplementary material available at 10.1007/s10620-023-07928-y.

Keywords: Artificial intelligence, Convolutional neural network, End stage liver disease, Liver transplantation, Artificial Intelligence enabled electrocardiogram, Receiver operator characteristic

Introduction

Cardiac events are a leading cause of morbidity and mortality after liver transplantation (LT). [1]. Consequently, a pre-transplant cardiac evaluation to screen for underlying cardiac disease and evaluate risk of future cardiac events is essential during assessment for candidacy for LT [2–4]. The pre-operative evaluation involves screening for underlying cardiac disease as well as evaluating the risk of future events [3]. The cardiac evaluation involves obtaining an electrocardiogram (ECG), chest radiograph, echocardiogram, and non-invasive stress testing. In selected patients, coronary angiography is performed if stress testing is abnormal, or coronary artery disease is suspected. Likewise, right heart cardiac catheterization is performed if pulmonary hypertension and elevated right ventricular systolic pressure are present.

Liver disease can directly aggravate cardiac function leading to systolic or diastolic cardiac dysfunction, pulmonary hypertension, and fluid retention. LT imposes major cardiovascular stress that can exacerbate or unmask any pre-existing cardiac dysfunction. Despite extensive pre-operative evaluation and optimization of a patient's cardiac status, cardiac events are the most common cause of death in LT patients with intact graft function. Cardiac events contributing to mortality early after LT include new onset systolic heart failure attributed to non-ischemic etiology or dilated cardiomyopathy occurring within the first few weeks of LT and arrhythmias [5, 6]. Pre-existing atrial fibrillation (AF) or new onset AF after LT may be associated with poor outcomes after LT, including heart failure, stroke, and death [7]. Moreover, the prevalence of post-transplant cardiac events has been rising [8]. The occurrence of peri-procedural and post-procedural cardiac morbidities highlight the need for improved risk assessment pre-LT.

Artificial intelligence (AI) based analysis using convolutional neural networks (CNN) applied to standard 12-lead ECG (artificial intelligence (AI) enabled electrocardiogram (AI-ECG)) can provide a low-cost, non-invasive screening tool for asymptomatic left ventricular dysfunction and propensity for those in normal sinus rhythm to develop atrial fibrillation in a general population. Their use as a screening tool to detect cardiac dysfunction has been validated in a general population, and in selected sub-populations such as individuals with Coronavirus disease 2019 (COVID-19) [9–14]. Advanced liver disease can cause hyperdynamic circulation that may cause cardiac remodeling and alter cardiac electrophysiology resulting in chronotropic incompetence and prolonged QT intervals. The resulting electrocardiographic changes may impact the utility of ECG based algorithms derived from patients without liver disease [10]. Thus, an assessment of the diagnostic utility of AI-ECGs within specific patient populations such as liver diseases is needed prior to their broader adoption. Given the interest in identifying subclinical cardiac disease prior to or after LT, our study sought to evaluate the performance of AI-ECG to screen for cardiac dysfunction and potential to develop post-transplant AF in persons with liver disease undergoing evaluation for LT or following LT.

Methods

Study Design

This was a retrospective single-center study of consecutive adult (recipient age ≥ 18 years) patients who were either evaluated for LT or underwent LT at Mayo Clinic in Florida between 2017 and 2019. Cases were identified from the transplant clinic database and the electronic medical record (EMR). Two non-overlapping study cohorts were defined. The first cohort A comprised of all patients who underwent LT between January 1, 2017 and December 31, 2018, and included all available studies before or after LT. The second cohort B comprised of all consecutive patients who underwent pre-transplant evaluation between January 1, 2019 and December 31, 2019. For this cohort, only studies performed as part of pre-LT evaluation were included. The study was approved by the Mayo Clinic Institutional Review Board.

Transplant Evaluation

Patient selection for LT was conducted by our transplant team following standard evaluation protocols consistent with American Association for the Study of Liver Diseases Guidelines on Evaluation for Liver Transplantation [2]. The pre-transplant cardiac evaluation protocol included an assessment of cardiopulmonary status with ECG, 2D transthoracic echocardiogram (TTE) and stress echocardiography, with invasive cardiac testing performed for higher risk patients as determined by a multidisciplinary transplant team. All ECG and TTEs were conducted at Mayo Clinic, obtained as part of the routine care of each patient, or within the specific context of pre-transplantation evaluation. For patients in cohort A (LT recipients), all available pre-transplantation and post-transplantation ECG and TTEs were analyzed. For patients in cohort B (LT evaluation), paired ECG-TTE data sets were created using ECG and TTEs that were performed within 30 days of each other and obtained during the evaluation for LT.

Transplant and Post-transplant Care

All liver grafts were procured from donation after brain death or circulatory death using standard procurement procedures. All patients undergoing LT received standard immunosuppression therapy per an established institutional protocol. Data on sociodemographic, clinical characteristics, comorbidities, and laboratory values were extracted from the EMR.

AI-ECG

The AI-ECG utilized a validated convolutional neural network-based algorithm trained to recognize patterns from eight independent leads (I, II and V1-6) from a standard 12-lead ECG which could identify the presence of left ventricular systolic dysfunction (LVSD) or intermittent AF but were not detectable by visual inspection [11]. The validated CNN used to detect electrocardiographic signatures for LVSD and AF, respectively, were trained on a total of 625,326 patients with paired ECG and TTE and 180,922 patients with 649,931 normal sinus rhythm ECGs. The details of this machine learning algorithm have been reported [9, 11–15] and were applied to each ECG used for this study without any additional training or optimization. ECGs were standard 10-s, 12-lead ECGs acquired in the supine position at a sampling rate of 500 Hz using a GE-Marquette ECG machine (Marquette, Wisconsin). For our analysis, we considered a prolonged corrected QT interval (QTc) in men as 450 ms or longer, and in women as 460 ms or longer [16].

Echocardiogram

Identified patients had 2-dimensional, Doppler, and/or 3-dimensional echocardiography. Left ventricular ejection fraction (LVEF) was estimated using standard methods recommended by the American Society of Echocardiography and the European Association of Cardiovascular Imaging. [17] Quantitative echocardiographic data were documented at the time of acquisition within a Mayo Clinic developed database (Echo Image Management System; Rochester, Minnesota).

Statistical and Data Analysis

AI-ECG predictions for chronological age, male sex, AF and low LVEF were outputted as proportions or percentages. We hypothesized that AI-ECG outputs from pre-transplant ECG that were above an arbitrary threshold or a threshold based on the derivation study would be associated with post-operative events. Assessment was performed with the use of the AI-ECG predictions as dichotomous variables and the discrimination for defined thresholds was determined. The predictive performance of the AI-ECG for male sex, chronological age, and post-operative events was evaluated by determining true and false positives and negatives based on the AI-ECG prediction probabilities at pre-selected threshold values and using the documented clinical and/or echocardiographic parameters in the medical record as gold standard. The values are reported along with their 95% confidence levels as appropriate. Predictive discrimination was determined by assessing the area under a receiver operator characteristic curve (AUROC), with an acceptable discrimination for AUROC > 0.5. Descriptive statistics were used for demographic or other data using either median and range or mean and standard error. The strength of the relationship between selected variables was evaluated using the Spearman's correlation coefficient (R^2). All analyses were performed using JMP®, version 14.1.0, SAS Institute Inc. NC, 1989–2019.

Data Availability

Data cannot be shared publicly because of patient privacy concerns. Data are available for researchers who meet the criteria for access to confidential data following approval by the Mayo Clinic IRB (www.mayo.edu). De-identified data can be requested through a Materials Transfer Agreement. Requests for patient-related data that is not included in the paper will not be considered. All requests for data will be reviewed by the Mayo Clinic Ventures, Business Development and Legal departments to verify whether the request is subject to any confidentiality restrictions or constitutes intellectual property.

Results

Study Cohorts

Two non-overlapping cohorts of patients seen at our center were included (Table 1). Cohort A was a transplant recipient cohort comprised of 300 consecutive patients undergoing LT over a 2-year period. For each of these patients, all available ECG and echocardiogram reports in the EMR were obtained spanning a time period from July 21, 1989 to December 8, 2020. There were 3202 ECG available, of which 1534 were obtained prior to transplant (ranging from 1 to 10,474 days pre-transplant), 383 on the day of the transplant and 1284 were obtained after transplant (ranging from 1 to 1322 days post-transplant). For this cohort, 719 echocardiograms were available for 300 patients. Of these, 523 were obtained pre-LT, and 196 were obtained post-transplant.

Table 1

Description of cohorts

	Transplanted patient cohort A (*n* = 300)	**Transplant evaluation cohort B (*n* = 412)**
Age in years: median (range) [25th percentile/75th percentile]	57.6 (19.7 to 75.2) [52.5–65.8]	59.9 (20.1 to 76.5) [53.5 / 66.5]
Males: number, %	191, 63.6%	241, 58.5%
History of CAD: number, %	61, 20.3%	58, 14.1%
ECGs	All pre-transplant and post-transplant studies	Single study per patient performed as part of pre-transplant evaluation
Number of ECGs	1917 prior to or on day of transplant/1284 post-transplant	412 prior to transplant
Echocardiograms	All pre-transplant and post-transplant studies	Single study per patient performed as part of pre-transplant evaluation
Number of echocardiograms	523 pre/196 post-transplant	392 (345 within 30 days of ECG)
MELD score: median (range)	21 (6 to 52)	14 (6 to 44)

Cohort B comprised of patients who underwent pre-LT evaluation. This cohort comprised of a consecutive group of 412 patients (171 females and 241 males) who underwent evaluation for LT during a 1-year period. Paired ECG and echocardiogram reports were available on 391 patients. Of these, 345 were obtained with 30 days of each other and were selected for further analysis. The MELD score at the time of evaluation ranged from 6 to 44 (Table 1).

How Well Does AI-ECG Perform in Patients with Liver Disease?

As an initial validation step, we began by first examining the performance of AI-ECG to determine subject demographics such as sex and chronological age in patients with liver diseases who were candidates for LT. For this assessment, we combined all available ECG in both cohorts A and B for a total of 3613 ECG (2298 from males, and 1315 from females). The types of rhythms reported are summarized in Table 2.

Table 2

Findings reported on ECG performed in study cohorts

	Transplanted patient cohort A $n = 3201$	Transplant evaluation cohort B $n = 412$
Normal sinus rhythm	2223 (69.4%)	312 (75.7%)
Sinus bradycardia	275 (8.5%)	55 (13.3%)
Sinus tachycardia	361 (11.2%)	24 (5.8%)
Marked sinus bradycardia	30 (0.9%)	7 (1.7%)
Atrial fibrillation	154 (4.8%)	4 (1.7%)
Atrial Flutter	36 (1.1%)	0 (0%)
Atrial tachycardia	3 (0.09%)	0 (0%)
Supraventricular tachycardia	4 (0.12%)	0 (0%)
Multifocal atrial tachycardia	2 (0.06%)	0 (0%)
Ectopic atrial, unusual P axis	23 (8.5%)	5 (1.2%)
Conduction abnormality	8 (0.24%)	0 (0.0%)
Ventricular tachycardia	2 (0.06%)	0 (0.0%)
Paced rhythm	34 (1.1%)	4 (0.97%)
Other	46 (1.4%)	2 (0.58%)

“Conduction abnormality” includes Non-specific intraventricular conduction block, Wide QRS rhythm, Wide QRS tachycardia, Junctional bradycardia, Junctional rhythm or Left bundle branch block. “Paced rhythm” included AV sequential, AV dual, atrial, atrial sensed ventricular paced, or dual chamber paced rhythms. The “other” group includes ECG where interpretation was one the following: poor data quality, baseline artifact, possible ST abnormality, possible lead reversal, non-specific ST abnormality, abnormal ECG, numerical interpretation, accelerated, low voltage QRS

First, we determined the utility of the AI-ECG for prediction of male sex (Table 3). An AI-ECG probability of male sex of 0.48 or more had 87.0% specificity and 76.1% sensitivity for prediction of males with an accuracy of 80.1% (95% confidence interval [CI] 78.7% to 81.4%). When applied only to ECG that were in sinus rhythm, there was only a marginal improvement in accuracy to 80.8%. Alterations in the QT interval, however, impacted AI-ECG performance. When applied only to ECG in sinus rhythm and had a normal QTc, the accuracy was improved to 81.8% (95% CI 80.0 to 83.5%) compared to an accuracy of 77.2% (95% CI 74.9 to 79.3%) in ECG that had a prolonged QTc. Notably, there was a difference in performance between ECG obtained pre-LT (accuracy 82.2%, 95% CI 80.4 to 83.9%) compared to those obtained post-LT (accuracy 77.6%, 95% CI 75.5 to 79.6%).

Table 3

Performance of AI-ECG for prediction of male sex

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value
All ECG	63.4% (61.4–65.3)	92.3% (90.8–93.7)	8.26 (6.83–9.98)	0.40 (0.38–0.42)	93.51% (92.3–94.6)	59.1% (57.7–60.4)
ECG with normal sinus rhythm	63.4% (61.0–65.8)	93.7% (92.0–95.1)	10.00 (7.85–12.73)	0.39 (0.36–0.42)	93.95% (92.4–95.2)	62.3% (60.7–63.8)
ECG with long QTc	57.4% (54.2–60.5)	92.1% (89.2–94.4)	7.26 (5.26–10.03)	0.46 (0.43–0.50)	94.15% (92.1–95.7)	49.4% (47.5–51.3)
ECG with normal QTc	68.0% (65.3–70.7)	92.1% (89.9–93.9)	8.56 (6.69–10.94)	0.35 (0.32–0.38)	93.00% (91.2–94.4)	65.0% (63.0–66.9)
ECG from pre-transplant patients	65.4% (62.7–68.1)	93.5% (91.5–95.2)	10.11 (7.62–13.41)	0.37 (0.34–0.40)	94.61% (93.0–95.9)	60.9% (59.0–62.8)
ECG from post-transplant patients	61.0% (58.0–63.9)	90.9% (88.3–93.1)	6.69 (5.18–8.65)	0.43 (0.40–0.46)	92.18% (90.1–93.8)	57.0% (55.0–58.9)

Performance of AI-ECG for prediction of male sex in liver transplant candidates. Values in brackets represent 95% confidence intervals

To examine the effect of sex-mismatch between donors and recipients, we performed an analysis on a subset of patients with sex-mismatch between donor organ and recipient. We excluded all ECG obtained on or before the day of the transplant. The performance of AI-ECG was similar in post-LT patients receiving either a sex-matched or sex-mismatched donor organ (Supplementary Table 1).

Next, we examined how well the AI-ECG model could predict chronological age. In the combined cohort group, the AI-ECG predicted age to within 10 years of actual age in 72.3% of all ECG (Table 4). The accuracy was similar (72.1%) in those ECG that had a normal QTc but was lower (68.9%) in those ECG with a prolonged QTc. In contrast, a small increase in accuracy was observed (73.7%) when the analysis was limited to those ECG with sinus rhythm only. The accuracy of the AI-ECG for pre-transplant patients was 71.6% and marginally lower in post-LT patients (70.9%). Together, these data support that the performance of the AI-ECG models for prediction of male sex and age was lower in ECG with prolonged QTc compared with normal QTc, and in post-LT patients compared with pre-LT patients.

Table 4

Performance of AI-ECG for prediction of age in liver transplant candidates

	Male			Female			All		
	Total number	% within 5 years	% within 10 years	Total number	% within 5 years	% within 10 years	Total number	% within 5 years	% within 10 years
All ECG	2298	40.5	71.8	1315	42.2	70.3	3613	41.1	71.3
ECG with normal sinus rhythm	1542	42.6	74.8	993	43.0	72.0	2535	42.6	73.7
ECG with long QTc	981	38.1	69.7	443	39.3	67.0	1424	38.5	68.9
ECG with normal QTc	1172	41.4	72.9	755	42.9	71.0	1927	42.0	72.1
pre-transplant patients	1235	40.7	72.2	711	42.8	70.5	1946	41.5	71.6
post-transplant patients	1063	40.3	71.3	604	41.6	70.2	1667	40.7	70.9

Can AI-ECG Predict Incidental AF During Normal Sinus Rhythm?

We examined the utility of AI-ECG analysis in sinus rhythm for the prediction of incidental AF (Table 5). In cohort A, 28 unique patients had either a pre or post-LT ECG with AF. Amongst 3201 ECG from this cohort, 2223 revealed sinus rhythm whereas AF was noted in 154 ECG (Table 2). On analysis of ECG in sinus rhythm, an AI-ECG probability of AF of 0.2 or more had a sensitivity of 96.1%, specificity of 52.3%, and accuracy of 65.7% (CI 61.33%-69.82%) for having at least one other ECG showing AF. Notably, the specificity in females, 66.7%, was higher than the specificity of 44.1% in males and in ECG obtained pre-LT (56.9%) compared with those obtained post-LT (48.7%). As with AI-ECG predictions of age and male sex, those from ECG with a prolonged QTc had a lower accuracy (64.8%) compared with those from ECG with normal QTc (66.4%).

Table 5

Performance of AI-ECG for prediction of Atrial Fibrillation

	Sensitivity	Specificity	Positive likelihood ratio	Negative likelihood ratio	Positive predictive value	Negative predictive value
All ECG	96.1% [91.7–98.6]	52.3% [46.9–57.7]	2.01 [1.8–2.3]	0.1 [0.0–0.2]	46.7% [44.1–49.8]	96.8% [93.2–98.5]
ECG with sinus rhythm	96.1% [91.7–98.6]	52.3% [46.9–57.7]	2.0 [1.8–2.3]	0.1 [0.0–0.2]	47.0% [44.1–49.8]	96.8% [93.2–98.5]
ECG from pre-LT patients	96.1% [86.5–99.5]	56.7% [48.6–64.6]	2.2 [1.8–2.7]	0.1 [0.0–0.3]	41.8% [37.4–46.5]	97.8% [91.9–99.4]
ECG from post-LT patients	96.1% [90.3–98.9]	48.7% [41.4–56.0]	1.9 [1.6–2.2]	0.1 [0.0–0.2]	50.0% [46.4–53.6]	95.9% [89.8–98.4]
ECG with long QTc	93.3% [85.1–97.8]	51.3% [43.2–59.3]	1.92 [1.6–2.3]	0.13 [0.1–0.3]	47.6% [43.4–51.9]	94.2% [87.3–97.5]
ECG with normal QTc	98.7% [93.1–100.0]	53.2% [45.8–60.4]	2.1 [1.8–2.45]	0.0 [0.0–0.2]	46.4% [42.6–50.2]	99.0% [93.5–99.9]
Male	97.1% [92.7–99.2]	44.1% [37.5–50.9]	1.7 [1.5–1.96]	0.1 [0.0–0.2]	51.9% [48.9–54.9]	96.1% [90.2–98.5]
Female	86.7% [59.5–98.3]	66.7% [57.7–74.8]	2.6 [1.9–3.6]	0.2 [0.1–0.7]	23.6% [18.4–29.8]	97.7% [92.0–99.4]

Performance of prediction of atrial fibrillation (AF) of an AI-ECG probability of AF > 0.2 on ECGs with sinus rhythm from all patients that had at least one ECG at any other time showing AF

How Effective Is AI-ECG in Pre-transplant Evaluation?

The effectiveness of AI-ECG as an adjunct for assessment of cardiac status in the pre-transplant population was examined. As part of an established assessment protocol, an ECG and 2D echocardiogram was obtained for all patients being evaluated for transplant listing. In the transplant evaluation cohort, we observed a close correlation between AI-ECG predicted age and chronological age, R2 = 0.9807 with 78.2% (270/345) of ECG predicted age within 10 years of chronological age (Fig. 1). Applying a higher AI-ECG cut-off of 0.7 or greater for prediction of male sex had a positive predictive value of 94.4% (95% CI from 89.6 to 97.1%). Performance was similar, but slightly worse in patients with MELD > 15 compared with those with MELD > 15. Individuals with lower EFs on TTE tended to have a higher AI-ECG prediction probability for low EF. All cases of LVEF < 50% on TTE were associated with a probability on AI-ECG of 0.2 or greater (Fig. 2).

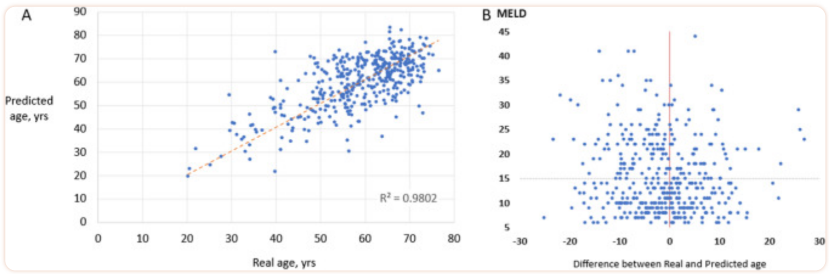


Fig. 1

AI-ECG based prediction of age. AI-ECG was performed in a cohort of 412 consecutive patients undergoing evaluation for liver transplantation. **A** The AI-ECG predicted age was correlated with real age. **B** The relationship between MELD score and the difference between real and predicted age. At MELD score less than 15, there was a greater correlation compared with at MELD > 15

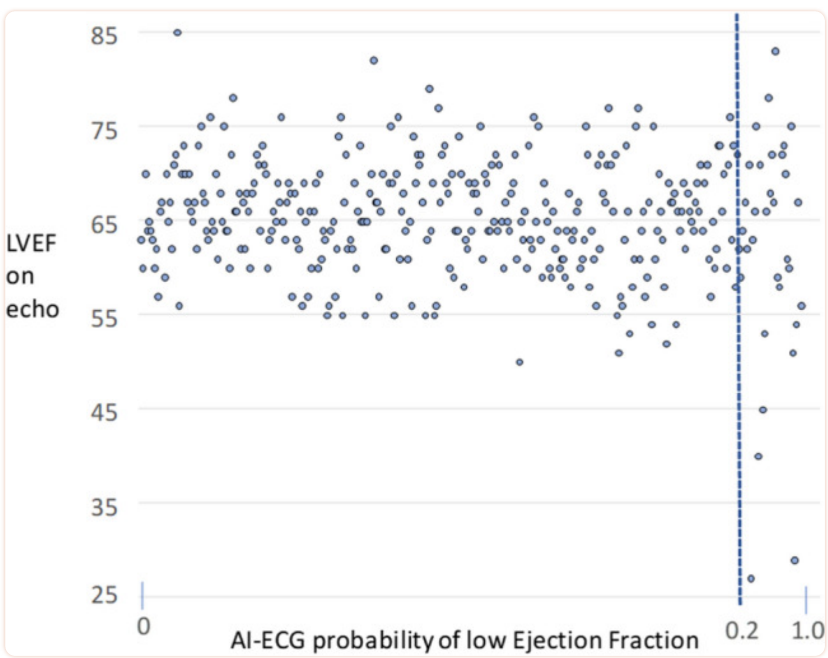


Fig. 2

AI-ECG based prediction of low ejection fraction (EF). Paired ECG and echocardiograms were obtained in 391 patients undergoing transplant evaluation. The left ventricular ejection fraction (LVEF) derived from echocardiography for each patient is plotted against AI-ECG probability of a low ejection fraction, in ascending order on the horizontal axis

Subsequently, we evaluated the ability of a pre-transplant ECG to predict the risk of developing new onset AF in the post-operative phase. In the transplant recipient cohort, 1666 ECG were performed in 300 consecutive patients on or after the day of LT. Of these, 103 ECG from 25 patients were noted to have AF. Amongst these, 15 patients had de novo AF post-LT and did not have any prior documented AF on pre-transplant ECG. Details of these patients are provided in Supplementary Table 2. The predictive ability of AI-ECG for de novo post-transplant AF was evaluated from an analysis of all prior ECG with sinus rhythm (Fig. 3). When analysis was limited only to pre-transplant ECG in sinus rhythm, AI-ECG had an AUROC of 0.63, with a probability of 0.182 or more had a specificity of 75.2% and sensitivity of 50.8% for prediction of new onset post-LT AF. The sensitivity increased to 63% and 73% using AI-ECG derived probability of AF cutoffs of 0.1 and 0.05, respectively (Supplementary Table 3). In a similar analysis on ECG in sinus rhythm obtained only from post-transplant patients, AI-ECG had an AUROC of 0.70 with a probability of 0.359 having a specificity of 86.2% and a sensitivity of 48.1% for the prediction of subsequent AF.

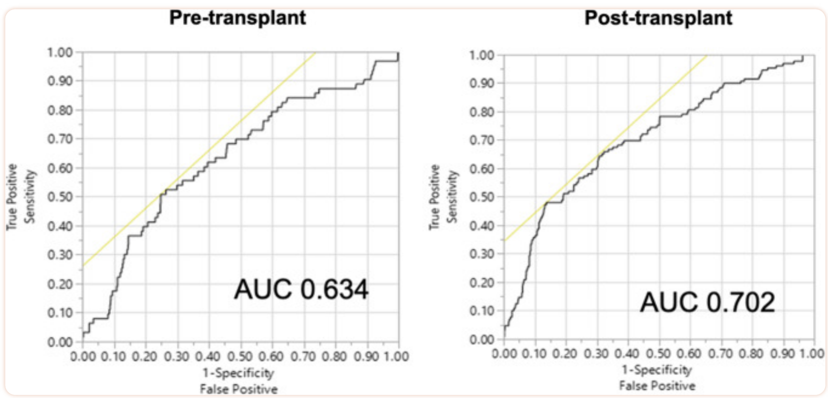


Fig. 3

Performance for prediction of post-transplant atrial fibrillation. AI-ECG analysis was performed on ECG showing sinus rhythm obtained (**A**) pre-transplant, with no prior ECG with AF, or (**B**) post-transplant, prior to onset of AF

Is Abnormal AI-ECG an Indicator of Subclinical Cardiac Dysfunction Leading to Low EF Post-transplant?

Post-operative cardiac dysfunction, as determined by reduction of LVEF to < 50% on echocardiography post-transplant occurred in 2.33% of LT recipients in cohort A (7 of 300 consecutive transplants). Details of these patients are provided in Supplementary Table 4. Amongst patients with post-operative cardiac dysfunction AI-ECG predictions of probability of low EF (pLEF) were higher, in aggregate, from ECG in sinus rhythm, sinus bradycardia or sinus tachycardia (Fig. 4). The AUROC for prediction of post-operative cardiac dysfunction was 0.69, with a predicted pLEF of 3.78 or more having a specificity of 71% and sensitivity of 56%. At a predicted pLEF of 0.7 or more, sensitivity for prediction of post-LT cardiac dysfunction improved to 94.9% but specificity was 28.6% with a positive predictive value of 11.8%, and negative predictive value of 98.2% (Supplementary Table 5).

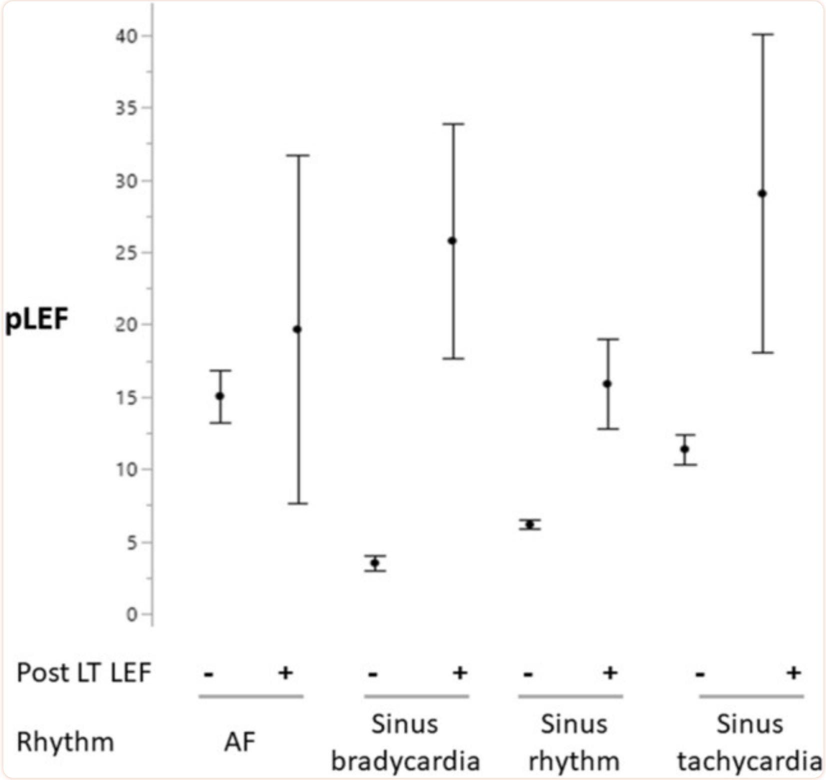


Fig. 4

Effect of rhythm on AI-ECG probability of low EF (pLEF). AI-ECG was performed in patients undergoing LT with or without a drop in EF to < 50 on echocardiography after transplant (Post-LT LEF). In aggregate, AI-ECG predictions of pLEF were higher in patients experiencing post-LT LEF from ECG in sinus rhythm, sinus bradycardia or sinus tachycardia

Discussion

In this study, we evaluated the performance of an AI-ECG algorithm in predicting cardiac events such as asymptomatic LVSD and incident AF during sinus rhythm in patients with end-stage liver disease undergoing evaluation or receiving a liver transplant.

Liver disease can be associated with altered cardiac electrophysiology resulting in chronotropic incompetence and prolonged QT intervals. Liver disease may directly aggravate cardiac function and can be associated with cardiac systolic or diastolic dysfunction, pulmonary hypertension and fluid retention. The resulting electrocardiographic changes may impact the utility of ECG based algorithms derived from patients without liver disease [10]. An assessment of the diagnostic utility of AI-ECGs within specific patient populations such as liver diseases is needed prior to their broader adoption.

The AI-ECG model used in this study was trained and validated to detect an AF signature even when the patient is in sinus rhythm. In the model derivation study, a single AI-ECG identified AF with an AUC of 0.87 and with a sensitivity of 79.0% and specificity of 79.5% [11]. This model predicted a cumulative incidence of future AF of 21.5% at 2 years in participants in a population-based cohort [18]. A different model derived from deep neural network modeling for prediction of new onset AF in patients with no history of AF had an AUROC of 0.82. In a simulated model, the sensitivity of this latter model was 69% and the specificity was 81% [19]. Our analysis revealed a specificity of 75% consistent with findings from these other studies and support the use of AI-ECG in patients without AF and in normal sinus rhythm for the prediction of post-operative AF even after a major procedure associated with significant hemodynamic and systemic metabolic perturbations.

Our results suggest that AI-ECG could be used to alert to underlying subclinical disease or left ventricular systolic dysfunction in persons with advanced liver disease prior to engaging in transplant evaluation (Fig. 2). Although the AI-ECG model was trained to detect low EF of < 50% at the time of the ECG acquisition, false positive screens by the AI-ECG were associated with a fourfold increase in the risk of future low EF over a median of 3.4 years in the original derivation study. Notably, a threshold prediction value of 0.256 or more detected LVEF of 35% or lower in the AI-ECG model derivation study in a general population. While a specific model trained to predict future risk of low EF in our patient population would be ideal, the low frequency of events reduce the data that available for training such a model. Nevertheless, our findings provide new information regarding the robustness of the AI-ECG model that broaden the potential utility and application beyond the original purpose. With our current transplant evaluation protocols for assessment of cardiac function, the prevalence of post-transplant cardiac dysfunction was only 2.33% in our patient cohort, consistent with reports from other centers [20]. In this context, any predictive test would be expected to have a low sensitivity. Consistently, AI-ECG based pLEF > 0.7 only had a positive predictive value of 11.76% for cardiac dysfunction post LT. Despite this, the ease of adoption of pre-transplant AI-ECG analysis could provide additional information that may identify patients needing closer monitoring of cardiac function in the peri- or post-operative period.

This study raises several questions that indicate directions for future studies. An assessment for underlying CAD is an essential component of pre-LT evaluation, efforts to derive AI based models for screening for CAD in these patients should be considered. Machine learning has been used to determine the risk of CAD in patients with diabetes [21], and the derivation of future models that also incorporate ECG based information for risk prediction in both diabetic and non-diabetic patients could be valuable for this purpose.

In this study, we examined the performance of an AI-enabled ECG analysis in patients undergoing evaluation for LT and identified factors impacting the performance of these models. Our study supports the use of AI-ECG for risk stratification pre-LT to identify individuals without symptomatic pre-LT cardiac dysfunction of AF but who may be at risk of developing these post-LT. We conclude that the use of the AI-ECG algorithm is a low-cost option for obtaining additional information regarding cardiac risk that can be readily implemented during transplant evaluation.

Supplementary Information

Below is the link to the electronic supplementary material.

Supplementary file1 (DOCX 20 KB)(20K, docx)

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Abbreviations

AF	Atrial fibrillation
AI-ECG	Artificial Intelligence enabled electrocardiogram
LT	Liver transplantation
CAD	Coronary artery disease
CI	Confidence interval
EF	Ejection fraction
EMR	Electronic medical record
ESLD	End stage liver disease
ECG	Electrocardiogram
LVSD	Left ventricular systolic dysfunction
CNN	Convolutional neural network
LVEF	Left ventricular ejection fraction
AUC	Area under the curve
pLEF	Probability of low EF on AI-ECG
ROC	Receiver operator characteristic

Author’s contribution

HZ, OM, TP, JR, JT contributed to data collection, JT, TP performed data analysis. HZ, TP drafted the manuscript. AK and DA provided expert input and reviewed the manuscript. All authors approve the final draft submitted.

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Declarations

Conflict of interest

There are no competing financial or non-financial interests to report.

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