Challenges of Deep Learning based Techniques for Detection of Potassium Imbalance from ECG:A Review

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Abstract

Chronic Kidney Disease (CKD) is rising at an alarming rate worldwide. The kidney's primary function is to maintain fluid and electrolyte balance. Any changes in renal function, whether acute or chronic, can cause multiple imbalances. In many cases, electrolyte imbalance, particularly potassium imbalance, has resulted in sudden cardiac deaths in such patients. Currently blood tests are conducted for measuring the electrolytes in patients. However continuous monitoring of imbalance or ease of such a test at home is not possible leading to life threatening conditions. Recent studies have found that electrolytes imbalance can be detected using ECG signals. ECG are commonly acquired during clinical examination and can now be easily acquired by many wearable sensors used for fitness and monitoring. ECG Interpretation requires expertise, however interpretation becomes difficult in cases where large amount of ECG data is being continuously generated by wearable sensors. Automatic interpretation of such ECG data would be useful especially in patients suffering from cardiac abnormalities. Machine Learning is a branch of Artificial Intelligence that allows computers to make accurate predictions. When compared to traditional or manual methods, the use of machine learning techniques, particularly deep learning, in ECG interpretation has demonstrated encouraging outcomes. In this review, we discuss the problem of electrolyte imbalance, explore the potential of ECG as a diagnostic tool and present the recent developments in using machine learning techniques especially deep learning for electrolyte imbalance detection using ECG. Further this paper also discusses the problem of interpretability of deep learning models and potential solutions offered by a relatively new field called Explainable AI. Finally the paper discusses the challenges faced by researchers in electrolyte imbalance detection using ECG

Keywords *Chronic Kidney Disease; Electrolyte Imbalance; Machine Learning; Deep Learning; ECG;*

DOINumber:10.14704/NQ.2022.20.11.NQ66014 **NeuroQuantology 2022; 20(11): 122-133**

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1Introduction

Kidney disease is one of the world's leading causes of death. Chronic kidney disease can progress to end-stage renal disease (ESRD), necessitating dialysis, a technique in which blood is removed from the body and purified by a machine.Rodrigues (2020) Hemodialysis and Peritoneal dialysis are the two types of dialysis procedures of which Hemodialysis is the most common form. As in these procedures actual kidney is not involved, physiologic regulation of both fluids and electrolytes is not possible, thus giving rise to problems such as electrolyte imbalances.Nanovic (2005)Dhondup (2017)JK(1987) Potassium imbalance is quite common in patients suffering from Chronic Kidney Disease.

Machine Learning is a popular subfield of Artificial Intelligence that allows machines to learn without being explicitly programmed. Various studies have utilized machine learning to automatically diagnose electrolyte abnormalities using ECG, however these models require handcrafted features to be presented to the model for classification. Deep Learning models have recently gained popularity and have been used in various fields for classification.Lahane(2021)Khan(2022)Kshirsagar(2022) Deep Learning models have automatic features extraction modules and hence result in better classification. Deep in deep learning refers to large number of hidden layers which help in learning highly complex nonlinear patterns from the data resulting in high accuracy in classification. However high complexity in these models make them hard to interpret. Explainable Artificial intelligence is a relatively new field of study that has evolved in the context of deep learning. The ability of a model to explain its results is referred to as explainability. It is usually inverse to its prediction accuracy. Turek(2017)

In this paper, we present a comprehensive review of recent machine learning models proposed for classification and detection of potassium imbalance. Section II gives a medical background needed to understand the relationship between electrolyte imbalance and its effect on ECG. Section III presents the potential of ECG as a diagnostic tool for detecting various cardiac abnormalities. Section IV discusses various machine learning and deep learning models used to detect potassium imbalance from ECG signals. Section V gives a brief introduction to the concept of explainability and presents various explainable models in literature for ECG diagnosis, and finally a discussion and conclusion of the paper are given in Section VI

2Medical Background

Electrolytes are minerals in the human body that are essential for good health. Fluid and electrolyte balance, electrical impulse transmission across cell membranes, nerve transmission, muscle function, and cognition are all dependent on sodium, potassium, magnesium, calcium, and chloride, as well as water.Shrimankar(2021) Arrhythmias, gastrointestinal problems, kidney dysfunction, endocrine disorders, circulatory diseases, lung illnesses, and acid-base imbalance are all causes of electrolyte imbalance in the human body.William L.Web(1981)Kidneys are vital organs in the human body that keep electrolyte balance in check. They filter electrolytes and water from the blood, returning some and excreting the rest in the urine. In those with chronic kidney disease and end-stage renal disease, electrolyte and acid-base imbalances are major causes of morbidity and mortality.JK(1987) Timely detection of such derangements like that of potassium will be useful in restoring the balance before the onset of arrhythmias. Currently electrolyte imbalances are identified using patient's blood sample. However testing of blood samples repeatedly is inconvenient, time consuming and cannot be done at home. Electrolyte imbalances influence the depolarization and repolarization of the cardiac cycle action potential by changing potentials across the cellular membrane of the cardiac myocytes.Diercks DB(2004)These changes in the cardiac cycle has incidental findings in the electrocardiogram

3ECG as a Diagnostic Tool

The electrocardiogram (ECG) is a common screening tool used by doctors. The ECG records the electrical impulses of the heart. The ECG shows a prominent pattern termed P wave, QRS complex and T wave that shows the heart's contraction and relaxation. Figure 1 shows the classical ECG waves. Any irregularity in the heart rate or rhythm disturbs this pattern, hence irregularities in heart rate and rhythm can be detected by monitoring the ECG. Heart attacks, inadequate supply of blood and oxygen supply to the heart can also be detected using ECG

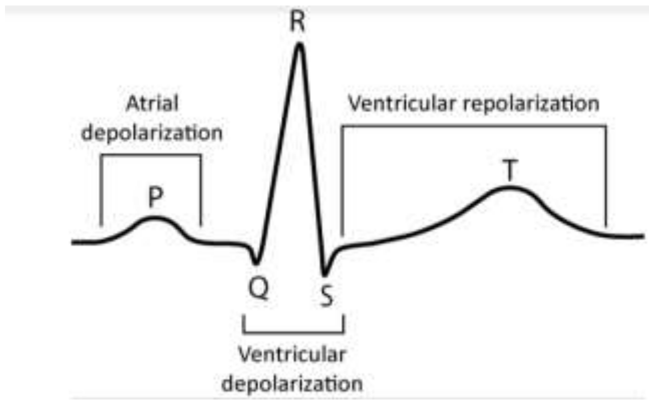

Figure 1: Classical ECG curves and events reflected by it. (*Image Courtesy: ecgwaves.com*)

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Electrocardiograms are commonly used by physicians to monitor patients' cardiac health. A 12 Lead ECG which is commonly used in hospitals provide the spatial information of this electrical activity of the heart. 1 Lead ECGs and 6 Lead ECG monitors are now easily available in most of the smart watches and fitness tracking systems. Apple Watch Series 4, 5, 6,Apple Inc(2021) Samsung Galaxy Watch 3 and Watch Active 2Samsung(2021), Withings Scan Watch,Withings (n.d.) Move ECGWithings (n.d.)and Fitbit senseFitbit LLC(n.d.) are some devices using 1 lead ECG. AliveCorsCardia Mobile 6LAlivcor(n.d.)provides 6 lead ECG, while Kardia MobileAlivcor (n.d.)is a 1 lead ECG. Interpretation of a patients ECG is not an easy task and requires expertise. Portable ECG generate massive data which may not be easy to interpret by medical experts due to limited time and resources hence automatic detection of ECG has been an area of research for over a decade now however the results cannot be relied upon Deotale(2021)Sathawane(2021)Macfarlane(2017). Table 1 presents recent attempts to detect Heart abnormalities in ECG.

Table 1. Automatic Heart Disease Classification

Year	Heart Abnormality	Database	Models	Reference
2021	Electrolyte Imbalance	Data from Sejong General Hospital (SGH),Korea	DLM with ensemble network	Kwon(2021)
2021	Atrial Fibrillation	The Sejong ECG dataset	CNN	Jo(2021)

2020	Normal Atrial Premature Beat, Premature Ventricular Contraction	MIT-BIH Arrhythmia Database	CNN	Avanzato(2020),Ullah,Rehman,Tu Mehmood & Fawad(2021)
2020	HeartBeat Classification	MIT-BIH, INCART	CNN	Romdhane(2020), Guoliang Yao(2021), Ramkumar(2021)
2020	Dyskalemias	Data obtained from Tri-Service General Hospital, Taiwan	CNN	Lin CS(2020)
2019	Multiple cardiovascular disease classification	MIT-BIH, St.-Petersberg, PTB databases, Dataset by iRhythm Technologies	1D-CNN	Hasan(2019), Hannun(2019)

4Classification of Electrolyte Disorders using ECG

The effect of electrolyte imbalances on the ECG can be influenced by a number of factors.

1) The electrolyte imbalances are superimposed on variations in the basic electrocardiographic patterns.

2) Nonspecific effects due to altered electrolyte concentration causing alterations in the rate or rhythm.

3) Repolarization changes as a result of intra-ventricular conduction abnormalities induced by aberrant electrolyte concentrations, and

4) Changes brought on by the action of one electrolyte on the concentration and activity of another electrolyte.Surawicz (1974)

Potassium is a very important cation which is found in the intracellular fluid in the human body. It is responsible for heart and cellular muscle contraction, nerve conduction and renal function. The potassium equilibrium potential determines the resting membrane potential of cardiac myocytes. Potassium levels that are either high or too low might cause difficulties in the heart muscle. The resting membrane potential is proportional to the ratio of intracellular to extracellular potassium concentration, according to the Nernst equation. Both high and low potassium have incidental changes in the ECG as reported in Table II.

Table II: Changes brought by potassium imbalance on the ECG

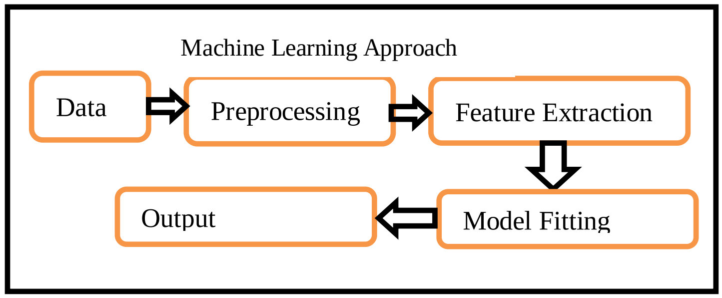
Electrolyte Imbalance	**Effect on ECG**
Hyperkalemia(5.5-6.5 mEq/L)	Thin, tall, narrow based and peaked T waves
Hyperkalemia(6.5-7.5 mEq/L)	P wave flattening, P-R interval prolongation, Widening of QRS complex
Hyperkalemia(>7.5 mEq/L)	P wave disappears and the PQRST is replaced by a smooth diphasic sine wave
Hypokalemia (<3 mEq/L)	T Waves that are wider and have lower amplitudes, T wave inversion, ST segment depression, and other symptoms may occur. P wave amplitude, P wave duration, and PR Interval all

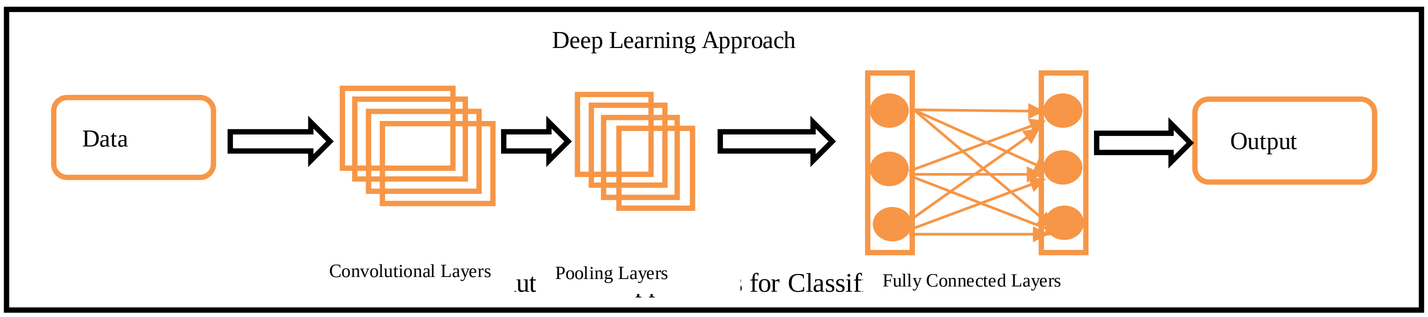
increase. U waves may appear, and they may be larger than T waves.

Many manual, semi-automatic and automatic approaches have been used by researchers for quantification or classification of potassium imbalance using ECG. Among them automatic approaches have shown promising results. Figure 2 depicts the steps involved in creating automatic models for ECG classification.

A retrospective study of 170 individuals with normokalemia and 135 patients with hyperkalemia was done by the authors inVarga(2019).Chronic renal disease affected 29 percent of the hyperkalemic patients. The most common and significantly more frequent ECG abnormalities suggestive of hyperkalemia in severely hyperkalemic patients compared to normokalemic persons were wide QRS, peaked T-waves, Ist degree AV-block, and bradycardia. Among them Wide QRS was most frequently occurring ECG alteration. The authors felt there were no significant alterations in some hyperkalemic patients. ECG Alterations in hyperkalemia were not significant in patients suffering from Acute Kidney Injury as reported in Regolisti(2020). The heart rate, intervals, ST deflection, and amplitude and length of the P, R, and T waves were all measured in 149 patients. The authors concluded that ECG changes were unreliable for detecting hyperkalemia in Acute Kidney Injury patients.In contrast, automatic methods have shown promising results in detecting hyperkalemia in patients. To predict hyperkalemia, a backpropagation neural network with two stages and 100 neurons in each hidden layer was built.Wu(2003) Seventeen features including T wave amplitude and duration from V1 to V6 leads from 50 patients were used as inputs to the first ANN in the first stage, and P wave amplitude, P wave duration, QRS duration, PR interval, averaged RR interval from lead II, and the output of the first stage network were used as inputs to the second ANN. The model had an accuracy of total 62.5% with sensitivity of 60%, specificity of 65% and was able to predict hyperkalemia more efficiently than experienced clinicians whose accuracy was only 50%. Low training data may have been the reason for low sensitivity of the model. In a follow up study using two stage k-means classifier the authors reduced the complexity of the model by reducing to five inputs. The two integrated T wave volumes of chest leads and limb leads were used as feature parameters for input to first stage classifier. In the second stage, PR interval, QRS duration, and QT interval were input as feature parameters. The classifier output was categorized into four classes of which one was for normokalemia and three of hyperkalemia. The classifier had an increased sensitivity of 85% and specificity of 79%. In this case also the training data considered was small, but however a less complex model may have yielded better sensitivity.

Constance *et al.,*used various machine learning models like SVM, K-nearest neighbor, decision tree and Gaussian Naïve Bayes to detect hyperkalemia from ECG data. Pwave, QRS complex, and T wave duration, as well as gender, age, blood potassium values pre and post dialysis, and the presence of known cardiac defects, were used to classify patients as normkalemic, hyperkalemic, or hypokalemic. Performance of Decision tree was observed to have classified better with 90.9 accuracy as compared to other models. Decision trees are relatively simple machine learning models with highly explainable outputs. However these simple models may not be able to capture the complexity of the data. High accuracy of decision tree could be due to the less amount of data used for training and testing. In the classification of ECGs, deep learning algorithms have demonstrated encouraging results





However these simple models may not be able to capture the complexity of the data. High accuracy of decision tree could be due to the less amount of data used for training and testing. In the classification of ECGs, deep learning algorithms have demonstrated encouraging results. Table III presents recent attempts to detect potassium imbalance from ECG using automatic methods. The deep layers capture the data's non-linearity, resulting in higher classification accuracy. Galloway *et al.*Galloway CD(2019) proposed a deep learning algorithm for detecting hyperkalemia in individuals with Chronic Kidney Disease. The model, a convolutional neural network with 11 layers, the first ten of which are convolutional and the last of which is a fully connected softmax layer, was trained using 1576581 ECGs from four (Lead I, II, V3, V5) and two (Lead I & II) leads of the ECG. The model was validated using three datasets collected from geographically different locations and showed a high AUC of 0.853 to 0.901 with 2 leads for identifying hyperkalemia in patients with CKD. The authors pointed out that using 4 leads(lead I,II,V3 and V5) the AUC was only 0.02 to 0.03 higher than using 2 leads (lead I & II). This is particularly important with respect to the ECG generated by fitness tracking systems or devices using lesser leads for self-monitoring. Additionally the authors performed feature visualization to understand how the network learns to detect hyperkalemia. They visualized the ECG changes that resulted in hyperkalemia prediction. It was observed that some ECG changes detected by network as hyperkalemia were not easily comprehended by human experts. A multi-classification model was proposed by Lin *et.al*Lin (2020)They proposed a deep convolutional neural network ECG12Net with 82 convolutional layers to detect dyskalemias. The system was trained using more than 50000 ECG from standard 12 lead ECG. The system was tested during a human machine competition and performed better than experts in detecting dyskalemias. The sensitivity for detecting hypokalemia and hyperkalemia were 50.7% and 50.8%. The specificities were 81.6% and 96.0%, positive predictive values (PPV) were 44.7% and 26.9% and negative predictive values (NPV) were 85.0% and 98.5% respectively. The authors go one step further to interpret their predictions using heat maps to visualize their results using class activation mappings and attention mechanisms which would help experts to understand the logic behind the models. The latest work was published in 2021 by Kwon *et.al.*Kwon(2021) They proposed a deep learning model for detecting electrolyte imbalance. An ensemble network was used. Each model was created using six residual neural network blocks, each having four stages that included two convolutional layers and two batch normalisation layers. The final layer of the sixth block was connected to a flattened layer that was fully connected to the 1D layer of neural nodes. The flattened layer's 1 DECG output, as well as the output of a Multilayer perceptron with three hidden layers, were sent into the first layer of the ensemble network, together with the age and sex of the patients. The second layer was connected to the output layer with two nodes which represented the probability of the electrolyte balance. Hypercalcemia, hypocalcemia, hyperkalemia, hypokalemia, hypernatremia and hyponatremia all had ROC-AUC values of 0.873, 0.857, 0.839, 0.856, 0.831, and 0.813. To address the class imbalance problem, oversampling and under sampling was performed on the training data. The data used in the study also contained information about multiple electrolyte imbalances which has not been addressed so far in any study. Multiple electrolyte imbalances may have varied effect on the ECG and is a much needed study.

TABLE III

Recent research using Deep Learning models for classification of potassium imbalance using ECG

Reference	ECG Leads	Task	Size of Training set	Size of Internal validation set	Model	Accuracy	Recall/ Sensitivity	Specificity	PPV	NPV	AUC-ROC
Galloway (2019)	I & II	K+	1576581	61965	CNN	76.1 - 80.4	78.1-80.5	75.2-81.3	13.8-18.1	97.6-98.5	0.85-0.88
Galloway (2019)	I & II	K+	1576581	61965	CNN	57.8 - 64.2	88.9-91.3	54.7-63.2	6.9-9.2	99.0-99.6	0.85-0.88
Galloway (2019)	I,II, V3,V5	K+	1576581	61965	CNN	77.4 - 82.6	81.3-84.0	77.1-84.2	11.0-15.4	98.9-99.4	0.88-0.90
Galloway (2019)	I,II, V3,V5	K+	1576581	61965	CNN	63.9 - 69.0	89.3-92.6	60.3-70.0	7.2-10.5	99.4-99.6	0.88-0.90
Lin(2020)	12	K+	28183	3993	CNN	NA	50.8	96	26.9	98.5	0.91
Lin(2020)	12	K-	28183	3993	CNN	NA	50.7	81.6	44.7	85	0.75
Kwon (2021)	12	K+	83449	12091	DLM with ensemble network	NA	0.901 (0.807 – 0.959)	0.850 (0.843–0.856)	0.038 (0.030 – 0.049)	0.999 (0.998 – 1.000)	0.945 (0.931 – 0.959)
Kwon (2021)	6	K+	83449	12091	DLM with ensemble network	NA	0.915 (0.825 – 0.968)	0.829 (0.822–0.836)	0.034 (0.027 – 0.044)	0.999 (0.998 – 1.000)	0.908 (0.894 – 0.922)
Kwon (2021)	1	K+	83449	12091	DLM with ensemble	NA	0.887 (0.790	0.866 (0.859–	0.042 (0.033	0.999 (0.998	0.903 (0.888

					network		– 0.950)	0.872)	– 0.054)	– 1.000)	– 0.918)
Kwon (2021)	12	K-	83449	12091	DLM with ensemble network	NA	0.893 (0.858 – 0.922)	0.704 (0.695–0.713)	0.100 (0.091 – 0.111)	0.994 (0.992 – 0.996)	0.866 (0.854 – 0.878)
Kwon (2021)	6	K-	83449	12091	DLM with ensemble network	NA	0.896 (0.861 – 0.924)	0.647 (0.638–0.656)	0.086 (0.077 – 0.095)	0.994 (0.992 – 0.996)	0.866 (0.854 – 0.877)
Kwon (2021)	1	K-	83449	12091	DLM with ensemble network	NA	0.930 (0.899 – 0.953)	0.465 (0.455–0.475)	0.060 (0.054 – 0.067)	0.994 (0.992 – 0.996)	0.797 (0.782 – 0.811)

5Explainable AI

Deep Learning models discussed earlier have shown promising results in classification of ECG as compared to machine learning models. However since features are extracted automatically in such models it is difficult to trace which features have contributed in the resultant classification. Hence real world implementation of such models become difficult and challenging as they cannot be trusted. Explainable AI is a relatively emerging research area that aims to uncover the deep learning black box. Explainable Models could be broadly classified as follows:

- Ante-hoc models or Post-hoc models-Ante-hoc models are interpretable by design. E.g. regression models, decision trees etc. On the other hand, post-hoc models are used to understand the results of black box models. Post-hoc interpretability can be further classified as follows based on what part the model explainsGuidotti R, 2018):
  - Model Explanation - Interpret the logic of the black box model.
  - Outcome Explanation - Interpret the reason behind the output of the model
  - Model Evaluation – Inspect how the output of the black box model varies with change in input.
- Model specific or model-agnostic: Model-specific interpretations are only applicable to that model. e.g. for neural networks while model-agnostic interpretations are independent of the model.
- Local or global: Local method interprets one prediction at a time while global methods attempts to interpret the entire model.

Most of the work reported in the field of ECG classification is limited to post-hoc models that employ local and model-specific interpretability strategies. LIMERibeiro MT(2016) and SHAPLundberg(2017) are two popular local, model agnostic, post-hoc models. They work by making small changes in the input to test the corresponding change in output predictions. If there is no significant change in the output prediction it would indicate that the input was not a significant predictor. Since they work locally, they pose a challenge for large datasets and do not correct the problems they revealRoss(2017). Selvaraju*et.al*Selvaraju(2017) developed Visual Explanations for CNN-based models. Gradient weighted class activation mapping (Grad-CAM) was a concept prediction method that used the gradients of ideas flowing into the final convolution layer to generate a coarse localization map highlighting the critical places in the image. Many researchers have been using the Grad-CAM model to produce visual explanations using Heat maps or saliency maps for ECG classification.Kwon(2021),Lin(2020). Ghazzemi*et.al* Ghassemi(2021) argues that even the most important parts of the heat maps may contain useful and non-useful information and simply localizing the area does not highlight what part of the region the model considered useful. The author stresses that Heat maps could be used as a means for model troubleshooting and systems audit thus contributing to improve model performance. CEFE was developed by Maweu*et.al*Maweu(2021), a modular framework for ECG signals that provides users with data descriptive statistics, feature visualization, feature detection, and mapping thus providing a functional understanding of the underlying module. Visual explanation provided by these models fail to provide the reassurance that the model is correct. Validation testing among a large diverse population is far more important for model testing.

6 Challenges&Concluion

This paper reviews recent algorithms proposed for monitoring electrolyte imbalances in chronic kidney patients using non-invasive techniques. Automatic methods using Machine learning and deep learning models have shown promising results as compared to semi-automatic methods or hand crafted techniques. Deep Learning models using automatic feature extraction have shown higher accuracy in classifying electrolyte imbalances. Many explainable models have been proposed so that users can trust the results of these models, however many open questions still remain. Limited Data availability remains a pressing problem for research in ECG classification for detection of potassium imbalances. Researchers and medical experts should work hand in hand to create a common ECG database from diverse population so that they are available for testing and validation of various proposed models. Code availability/Model availability will help to reproduce results and enable comparison of various models. Using 12 lead ECG data have shown to improve classification accuracy however research using lesser leads is required to encourage creation of portable devices for monitoring potassium imbalance in CKD patients. Although explainability techniques are being proposed, they are yet to provide the "trust" and justifications for the results. Explainability techniques can be used as a means for models audit rather than testing the correctness of the model. Their role in AI safety is an open research problem.

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