Cardiorenal Interaction Assessment via ECG Features: A Study using Dynamic Time Warping and Extracted Feature Clustering

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Submitted to: Journal of Medical Internet Research
on: March 03, 2025

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Abstract

Background: The heart and kidneys have vital functions in the human body that reciprocally influence each physiologically and pathological changes in one organ can damage the other. Epidemiologic studies show that greater than 50% of patients with heart failure (HF) have preserved ejection fraction (HFpEF). Additionally, one in six patients identified as having chronic kidney disease (CKD) also has HF. Thus, it is important to be able to predict and identify the cardiorenal relationship between HFpEF and CKD.

Objective: Creating an ECG-enabled model that stratifies HFpEF suspected patients would help identify CKD enriched HFpEF clusters and phenogroups. Simultaneously, a minimal set of significant ECG features derived from the stratification model may aid precision medicine and practical diagnoses due to being more accessible and widely readable than a large set of clinical inputs.

Methods: Using unsupervised clustering on all extractable ECG features from FinnGen, patients with an indication of HFpEF (filtered by LVEF ? 50% and NT-proBNP > 450 pg/mL) were categorized into different phenogroups and analyzed for CKD risk. After isolating significant predictive ECG features, unsupervised clustering and risk analysis were performed again to demonstrate the efficacy of using a minimal set of features for phenogrouping. These clusters were then compared to clusters formed using Dynamic Time Warping (DTW) on raw ECG time series electrical signals. Afterwards, these clusters were analyzed for CKD enrichment.

Results: Several HFpEF clusters exhibited a deviation of CKD risk from baseline which may allow for further trajectory analysis. The DTW generated clusters were more stable than either sets of clusters formed on the minimal set of extracted ECG features or all extracted ECG features. PR interval and QRS duration stood out as significant features.

Conclusions: This project validates both the known cardiorenal relationship between HFpEF and CKD and the importance of the PR interval and QRS duration. DTW clustering may be capable of phenogrouping and patient stratification for CKD enrichment in HFpEF patients.

(JMIR Preprints 03/03/2025:73353)
DOI: https://doi.org/10.2196/preprints.73353

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Cardiorenal Interaction Assessment via ECG Features: A Study using Dynamic Time Warping and Extracted Feature Clustering

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Abstract:

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Keywords:

Data analysis; clustering; electrocardiogram; heart failure; renal insufficiency, chronic; ECG;

cardiorenal

Introduction

This manuscript examines the relationship between a specific sub-type of heart failure (HF), heart failure with preserved ejection fraction (HFpEF) and chronic kidney disease (CKD) marked by progressive renal failure [1–3], emphasizing the pathophysiological connections. It explores the potential use of technologies in trials and clinical management by leveraging simple and widely accessible clinical tools such as ECGs to predict the underlying risk in subgroups and to enable earlier and more precise interventions that can improve patient outcomes chronic diseases of cardiovascular and or overlapping renal origin [4–6] .

Heart failure (HF) and renal failure are two interrelated conditions that often coexist, significantly impacting patient outcomes [7–9]. The intricate and bidirectional relationship between the heart and kidneys, often referred to as the cardiorenal nexus, underscores the significant unmet need to understand how dysfunction in one organ can precipitate or exacerbate dysfunction in the other, so that patients at risk for progression can be precisely diagnosed for earlier intervention before full onset of disease thus improving the odds of better patient outcome[10] .

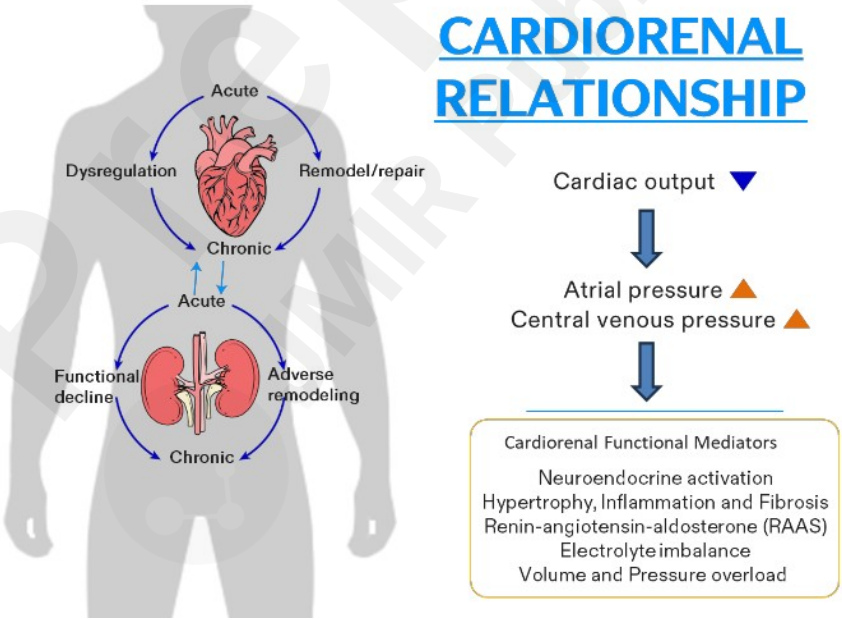

Figure 1: Illustration of the cardiorenal relationship and functional mediators.

HF, which is marked by the heart's inability to pump blood effectively, initiates a series of physiological changes that can negatively impact renal function. Reduced cardiac output in HF leads to decreased renal perfusion, triggering compensatory mechanisms such as the activation of the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system [11,12] .

Although these mechanisms initially aim to preserve renal function and maintain blood pressure, their chronic activation can produce adverse effects, including increased sodium and water retention, further worsening heart failure symptoms and contributing to renal impairment [13,14]. HFpEF is characterized by the heart's inability to relax (diastolic defect) and fill properly, leading to heart failure symptoms despite a normal ejection fraction (systolic function).

Conversely, renal failure can significantly affect cardiac function. The kidneys regulate fluid and electrolyte balance, blood pressure, and the elimination of metabolic waste products. When renal function declines, fluid overload, electrolyte imbalances, and the accumulation of uremic toxins can occur, adding strain on the heart. This may lead to worsening heart failure, creating a cycle of deteriorating cardiac and renal function. This bidirectional nature of the heart-kidney interaction underscores the complexity of managing patients with both heart failure and renal failure. The ability to better predict risk in these vulnerable cohorts would be beneficial for disease understanding and clinical trial recruitment.

Recent advancements in artificial intelligence (AI) and machine learning have shown potential in predicting and managing the risks associated with cardiorenal syndrome. AI-enabled models, for example, using ECG and biomarkers have demonstrated promise in clinical care settings [15,16].

An additional use of such an ECG model in drug development could be to identify HFpEF patients [17] who may demonstrate a potential risk profile for worsening kidney function based on screening ECG. Such patients may demonstrate other comorbidities such as hypertension, diabetes or obesity as stated earlier. This underlying and hidden risk can be revealed early for an improved understanding of associated risks with renally cleared cardiovascular drugs. The cardiac-specific electric signals provide significant discriminatory power for endo-phenotyping within the broader HFpEF spectrum [18] . By leveraging machine learning-based unsupervised cluster analysis, this study aims to phenomap patients with HFpEF, enhancing the understanding and prediction of cardiorenal risk through a generalizable and interpretable ECG-based machine learning model.

Clustering Cohort Baseline Characteristic Values

Characteristic	Value (mean)
Age (years)	71.16 ± 11.32
Women (%)	48.5
BMI	28.4
NT-proBNP (pg/mL)	2018.1
LVEF (%)	60.25
Creatinine (µmol/L)	103.02
Height (cm)	170.3
Weight (kg)	82.7

Current Smoker (%)	12.3
Chronic Kidney Disease (%)	1.6

Table 1: A characteristics average table to give better understanding of the clustering cohort. This cohort is comprised of individuals that have characteristics that indicate HFpEF (LVEF ≥ 50% and NT-proBNP > 450 pg/mL).

Evaluating the importance of ECG features for unsupervised clustering can be difficult. A lot of tabular health care data, including the extracted ECG features, are highly correlated which may lead to poor clustering results in practice. This also makes feature selection through Lasso very difficult. Used for building models, Lasso is a regression technique that helps in selecting explanatory variables by ranking their coefficients. Reducing dimensionality often makes interpretability difficult as well, which is especially an issue for healthcare research. Thus, finding an unsupervised method that clusters high dimensional correlated data through feature selection rather than dimension reduction would be very helpful [19].

Dynamic time warping (DTW) measures the similarity between two temporal sequences and, thus, can be used as a metric for clustering temporal sequences. By creating a non-linear alignment of time sequences that are of different lengths or exhibit time-shift, it can calculate the euclidean distance between points of the two warped sequences. DTW has been frequently used for longitudinal and trajectory analysis including in healthcare settings[20]. Due to the temporal nature of ECGs, DTW has been used to classify ECG frames and has been shown to be effective in finding nonlinear clusters of ECGs [21]. Previous literature and studies for DTW ECG clustering uses the Lead II recording wavelengths due to the Lead II wavelength being generally considered the best view of the electrical signals because of the electrode's placement [20].

ECGs also come with extracted features that have clinical relevance and meaning. Certain elements of the Lead II wavelength correspond with these extracted features; by being able to compare these features in the clusters created by DTW application on the wavelength itself, feature selection could occur by evaluating ECG signals or extracted features that contribute the most to the DTW's similarity formula.

Clusters generated by DTW from ECGs have not been further studied for phenotyping. Specifically, the relationship between extracted ECG features (e.g. PR interval, QRS duration, P axis, etc.) and these DTW clusters is not known. Neither have these clusters been analyzed for CKD enrichment. Understanding the relationship between these factors through the lens of DTW clustering could lead to better biological understanding. Combining the stability of the DTW created clusters with the interpretability from extracted ECG feature analysis may better the understanding of the cardiorenal relationship in particular.

ECGs are particularly appropriate for this combination of DTW-supported unsupervised clustering and feature analysis. Firstly, the assumption that

patients themselves, rather than the extracted ECG values, are independent and identically distributed is much easier to meet. This may make unsupervised clustering results more promising than on extracted ECG data (which would be correlated tabular data). By treating each ECG record as a singular data point, we can perform Dynamic Time Warping (DTW) on the ECG as a time series. DTW is a technique that calculates the optimal match between given sequences (it can be thought of as clustering curves via distance rather than individual data points). This way, different "clusters" of ECG records can be formed and then analyzed for disease endpoint incidence, cluster stability, and other performance metrics.

Many studies focus on the relationship between HFpEF and electrocardiographic (ECG) features, but our work attempts to explore the cross-organ interactions between the heart and kidney in HFpEF, by use of an algorithm that leverages specific ECG features which may serve as novel predictors of cardiorenal risk. Small changes in electro conductance system of the heart can have a big impact of the hemodynamic load on the heart exacerbating the load and over time, affecting volume overload [10] on the kidneys. However, such small changes in ECG, which may appear early, may not always be clinically apparent and can be often missed. In HFpEF patients clinical phenotype can be associated with diabetes, hypertension and obesity [22] . Using an ECG model to identify non-obvious, subtle patterns in the electrical signals of the heart captured through a standard electrocardiogram (12 leads) can indicate left ventricular (LV) dysfunction associated with HFpEF and can potentially also recognize renal-risk signals in a subset of patients.

Methods

Dataset Description

The FinnGen study is a large-scale genomics initiative that has analyzed over 500,000 Finnish biobank samples and correlated genetic variation with health data to understand disease mechanisms and predispositions. The project is a collaboration between research organizations and biobanks within Finland and international industry partners [23]. This public-private partnership aggregates data from 9 different Finnish biobanks, research institutes, university hospitals, and 13 international pharmaceutical partners along with the Finnish Biobank Cooperative (FNBB). Sample collection and data releases began in 2017 and the main phase of sample collection ended with FinnGen2 in 2023.

The Expansion Area 3 (EA3) studies aim to collect data on diseases that may not be present within existing FinnGen registries. Among this data is the EA3 Heart Failure Study cohort which compiles relevant cardiovascular data from 4-6 participating hospital biobanks. The study contains ECG files, ejection fraction values (40,809 individuals), and laboratory measurements (40,024 individuals) with BNP, proBNP, and creatinine values. Since the study is aggregated from several different existing biobanks, not all individuals have the same lab measurements. This project used the EA3 Heart Failure study individuals with

ECG, ejection fraction, and labs with creatinine and proBNP values all present.

The methods for extracting relevant features are changing and evolving over time [24] but the idea remains the same. The ECG follows a characteristic PQRST wave that occurs in a periodic pattern. Each peak, trough, or section of this wave represents electrical signals of the heart and can be evaluated for further meaning. Clinicians can look at the ECG visually for meaning but signal processing techniques can also retrieve the mathematical values from the waves themselves. Since there are multiple electrodes for measuring the ECG, this is usually taken from Lead II or aggregated.

Data Preprocessing

The dataset was restricted to the HFpEF population. This was determined by selecting individuals with ejection fraction values greater than or equal to 50 and exhibiting heart failure at that time. Exclusively ECGs recorded within a six-month period of the heart failure diagnosis or lab indicative of heart failure were used in this study. Creatinine values were used to determine the presence of CKD. The EA3 Heart Failure Cohort contained 1626275 lab records for 40024 unique individuals. Among these, there were 7170 complete ECG (extracted ECG values and raw ECG signals) and creatinine lab records for 3864 unique HFpEF individuals.

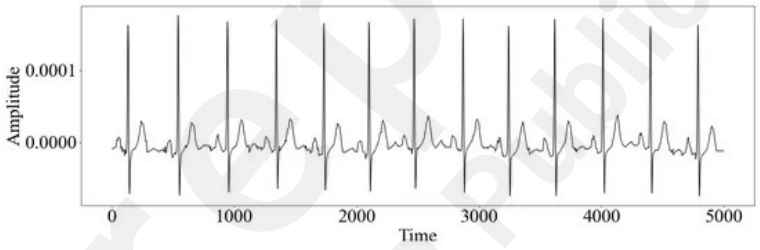

Figure 2: A sample Lead II ECG wave[25] .

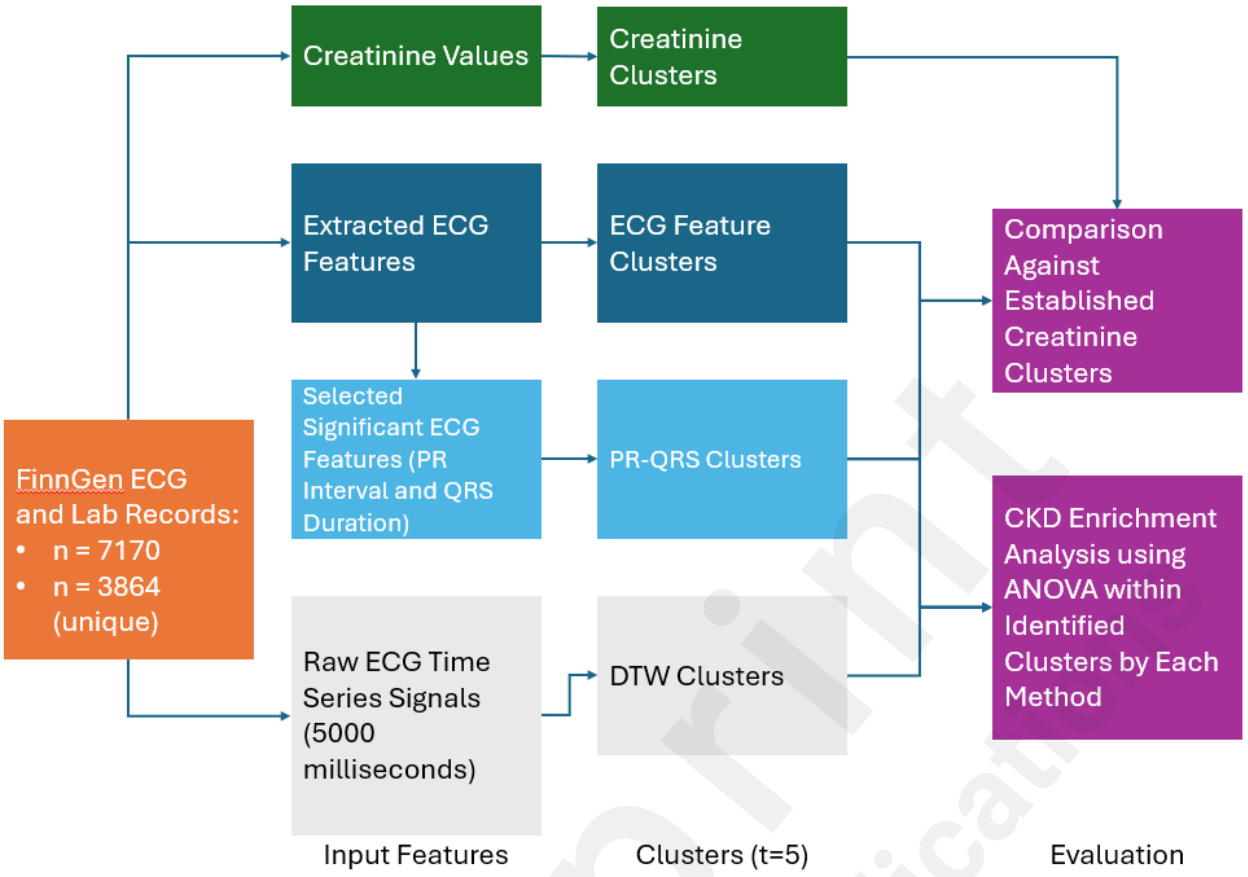

Figure 3: An illustration of the methodology workflow. FinnGen ECG and lab records are used to create different sets of clusters: Creatinine clusters (hierarchical clusters based off creatinine labs to be used as a baseline indication for CKD), ECG feature clusters (clusters created using all extracted ECG features), PR-QRS clusters (clusters created using top variables determined to be significant in predicting CKD in HFpEF), and DTW clusters (clusters created using DTW on the raw ECG time series). For each set of clusters, 5 groups were formed.

Statistical Analysis

Univariate analysis was first performed for exploratory purposes. Distributions and averages of the extracted ECG values (i.e. Ventricular Rate, PR Interval, QRS Duration, QT corrected, P axis, R axis, T axis, QRS count, Q onset, Q offset, P onset, P Offset, T Offset, Atrial Rate, QT Interval) were calculated. A T-test was conducted for all extracted ECG variables to determine if there was significant difference between non-CKD and CKD HFpEF patient ECG values. The results indicated that all extracted features were indeed different with a significance level of 0.05. Survival analysis was also conducted using a Cox Proportional hazard model and a Kaplan Meier curve.

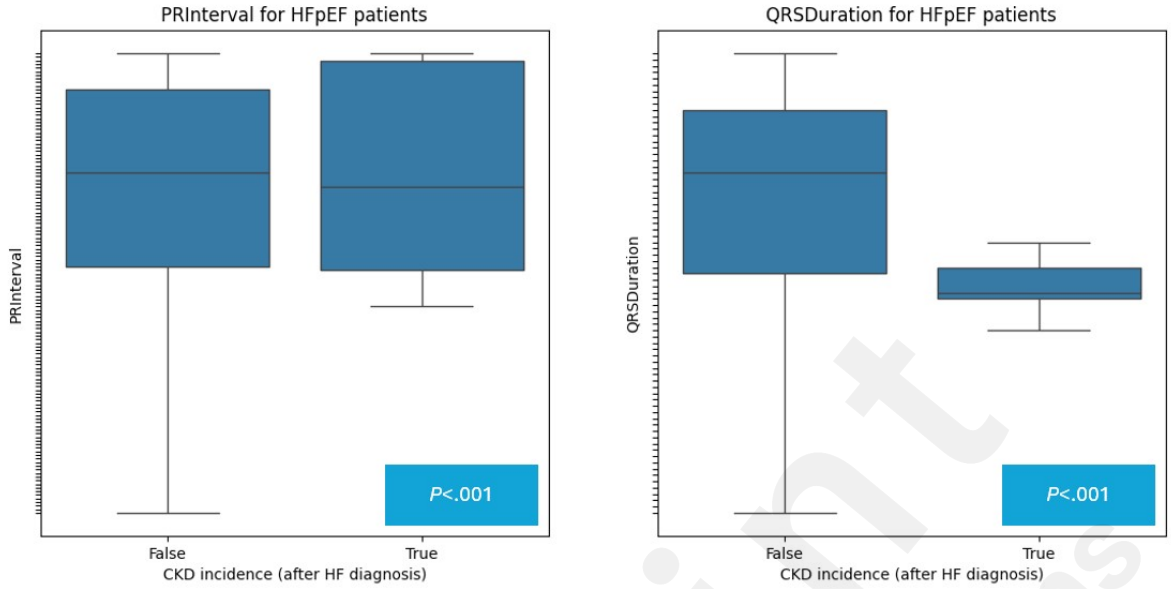

Figure 4: Distribution of significant extracted ECG values (QRS Duration and PR Interval) between CKD positive and negative patients.

Multivariate analysis of the extracted features was also conducted. It must be noted that the method may not be wholly accurate because of the correlation between the extracted features are derived from the ECG waveform itself and can have some overlap (see Figure 5). It is important to note that the method may not be wholly accurate because of the correlation between the extracted features. Additionally, these features lose some information in terms of the time component. However, it provides good exploratory insight into which combination of features would perform well for both CKD prediction and patient phenotyping.

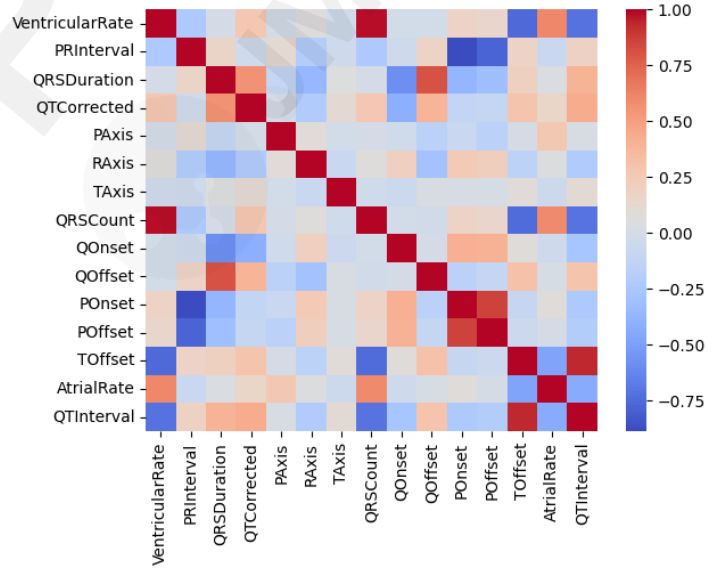

Figure 5: A heatmap showing the correlation between extracted ECG features.

Determining Number of Clusters

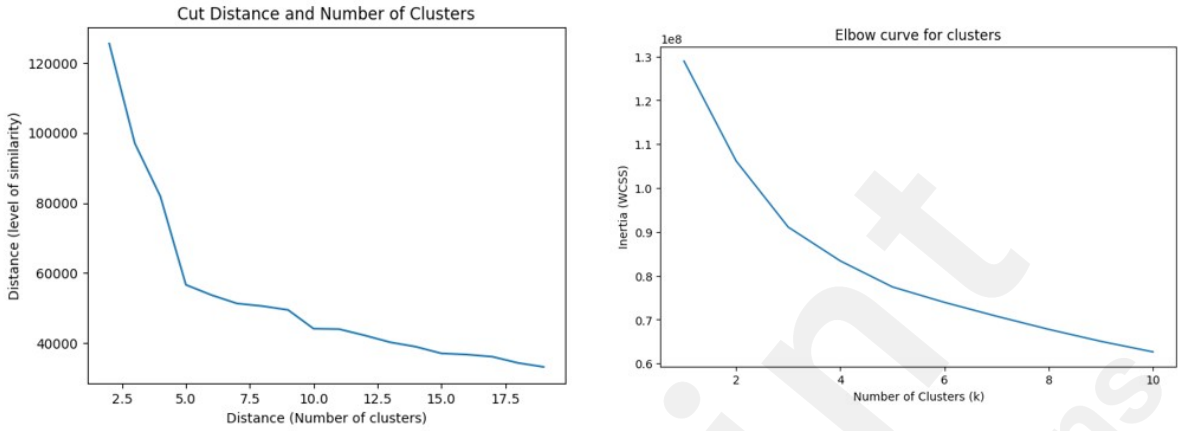

Figure 6: Elbow curves for extracted feature and DTW hierarchical clustering. This was used to determine the optimal number of clusters (t=5). The number of clusters was determined using these elbow charts and by seeing where the reduction in inertia or cut threshold has diminishing returns.

To determine the number of clusters created, elbow curves were created and analyzed to determine which number of clusters would be optimal. As both elbow charts exhibit diminishing returns at around the five cluster mark, it was determined that five clusters would be generated and compared.

Extracted Feature Clustering

Several methods were used, including PCA, significance, and Lasso feature selection. Relevant hyperparameters (e.g. alpha for Lasso dropout) were tuned iteratively to find the top five (five is pre-defined) features. For PCA, 50 simulations were run for stability and robustness purposes. In every simulation, the FinnGen data was randomly sampled (training=0.8, 80% from all data) and PCA was conducted on this random sample to select for the top five ranked features. From the repeated PCA analyses, the top five features that explain variance in order are: Ventricular Rate, PR Interval, QRS Duration, QT Corrected, and P axis. As for Lasso regression, the top features were QRS Duration, QT Interval, R Axis, QT Corrected, and PR Interval. In terms of significance, the top features were Ventricular Rate, PR Interval, QRS Duration, QT Corrected, and P axis. This exploration consistently identified PR Interval and QRS Duration as top features.

PCA Analysis

PCA Component	ECG Variable	Average Explained Variance
0	Ventricular Rate	0.276
1	PR Interval	0.251
2	QRS Duration	0.156
3	QT Corrected	0.122
4	P Axis	0.091

Table 2: A table ranking component (ECG variable) importance by average explained variance. PR Interval and QRS Duration are among the top 3 extracted variables. Ventricular Rate was not chosen because it was not selected among the top 5 features during Lasso regression.

However, despite bootstrapping for stability and generalizability, the clusters formed from PR Interval and QRS Duration had low stability and consensus despite performing better than clustering on all features. This is probably due to the correlated nature of the extracted ECG features. Thus, hierarchical clustering using Dynamic Time Warping distance calculations were also performed to consider the correlation.

Dynamic Time Warping (DTW) Clustering

The ECG lead II data was split into a training, validation, and test sets, each with 500 different unique individuals. Every patient's Lead II data included 5000 signals. These were then clustered using hierarchical clustering with Ward's method. Ward's method was chosen because it is close in functionality to K-means which makes it intuitive and interpretable. However, it also performs better than K-means on uncovering clusters of uneven size and irregular non-spherical clusters. Exploratory analysis has shown the clusters to be uneven and not guaranteed to be regular which makes Ward's method fitting.

The distance between each time series was determined using DTW. The algorithm calculates the Euclidean distance between each point in two time series after taking into account alignment of the time series. It returns the minimum distance between the two time series by shifting the time series so that distance is minimized. For the regular ECGs, little shift needed to occur due to the similarity of the wavelengths.

Average creatinine values associated with ECGs were calculated for every cluster. The average creatinine value of the HFpEF population was 103.02 umol/l. For the non HFpEF population, the average creatinine value was 92.44 umol/l.

Creatinine Clusters

Since the clusters were generated using an unsupervised method, there was no definitive baseline for comparing the cluster labels. Therefore, we created five clusters using hierarchical clustering based on creatinine lab values to serve as a reference. Being a waste product from muscle and protein breakdown, creatinine levels can serve as an estimation of kidney function and a metric for CKD. Thus, comparing the extracted ECG value and DTW formed clusters to

these creatinine-based clusters can demonstrate the former's capabilities in demonstrating creatinine enrichment and, subsequently, CKD enrichment.

Cluster stability was measured using silhouette score [26] and co-cluster occurrence (Jaccard score) and Rand index [27] . For the hierarchical clustering on DTW determined distance, Jaccard index was determined to be a more relevant metric than silhouette score. Compared to naively clustering on extracted features, the clusters were shown to be more stable.

Average features were calculated for every ECG cluster. ANOVA was conducted to determine any significant extracted feature difference between the clusters.

Results

Clustering on Extracted ECG Features

The top two features determined are QRS Duration and PR Interval. Both of these features were uniquely among the top five ranked features in every method used (significance, lasso, PCA).

Although there is a difference between CKD incidence when clustering on all available ECG features compared to clustering on the significant ECG features (PR interval and QRS duration), the difference may be too small to be clinically significant.

Clustering with Dynamic Time Warping

Regardless of how many clusters the parameter is set for with hierarchical clustering, clustering with DTW consistently yielded approximately five groups. This phenomenon could be seen in both the testing and validation sets and also when bootstrapping.

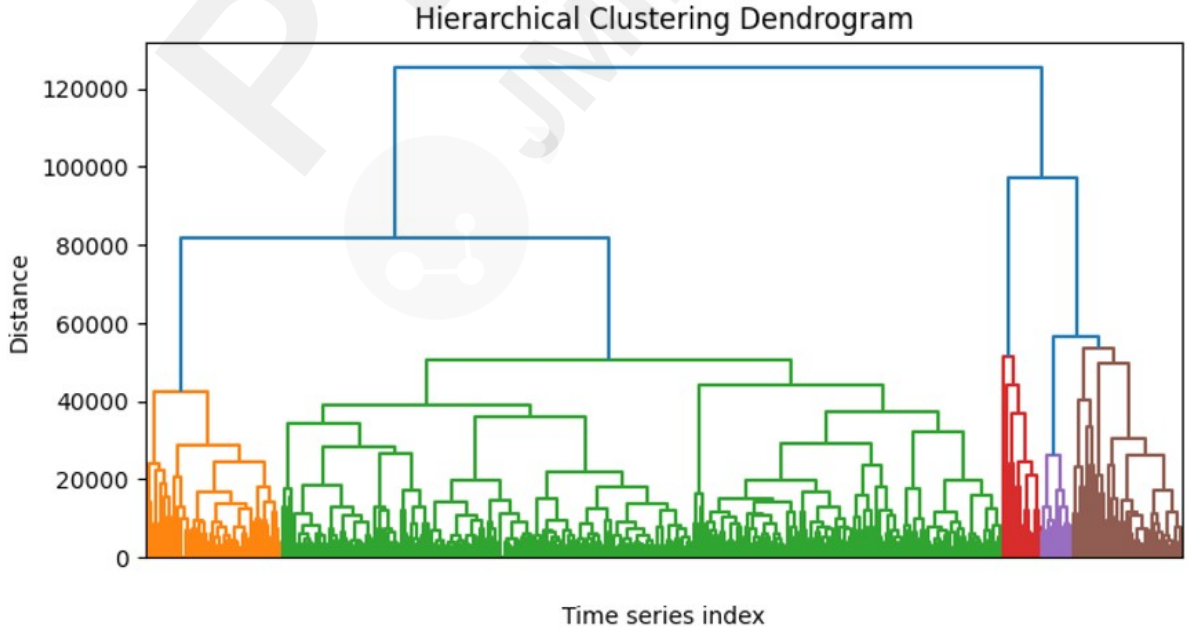

Figure 7: Hierarchical clustering on the validation set. We can see that approximately five clusters form which match up to the number of clusters estimated using the elbow method on the extracted ECG values. Due to the number of time series that were clustered, there were too many labels to list individually.

ECG Variable	F-stat	*P*-Value
Ventricular Rate	46.945	<.001
PR Interval	2.466	.062
QRS Duration	42.311	<.001
QT Corrected	14.901	<.001
P Axis	.498	0.684
R Axis	61.873	<.001
T Axis	.226	.878
QRS Count	47.793	<.001
Q Onset	15.444	<.001
Q Offset	28.054	<.001
P Onset	5.614	.001
P Offset	3.295	.020
T Offset	28.427	<.001
Atrial Rate	14.475	<.001
QT Interval	29.769	<.001

Table 3: ANOVA test on all extracted ECG values between the 5 clusters identified in ECG Feature Clusters.

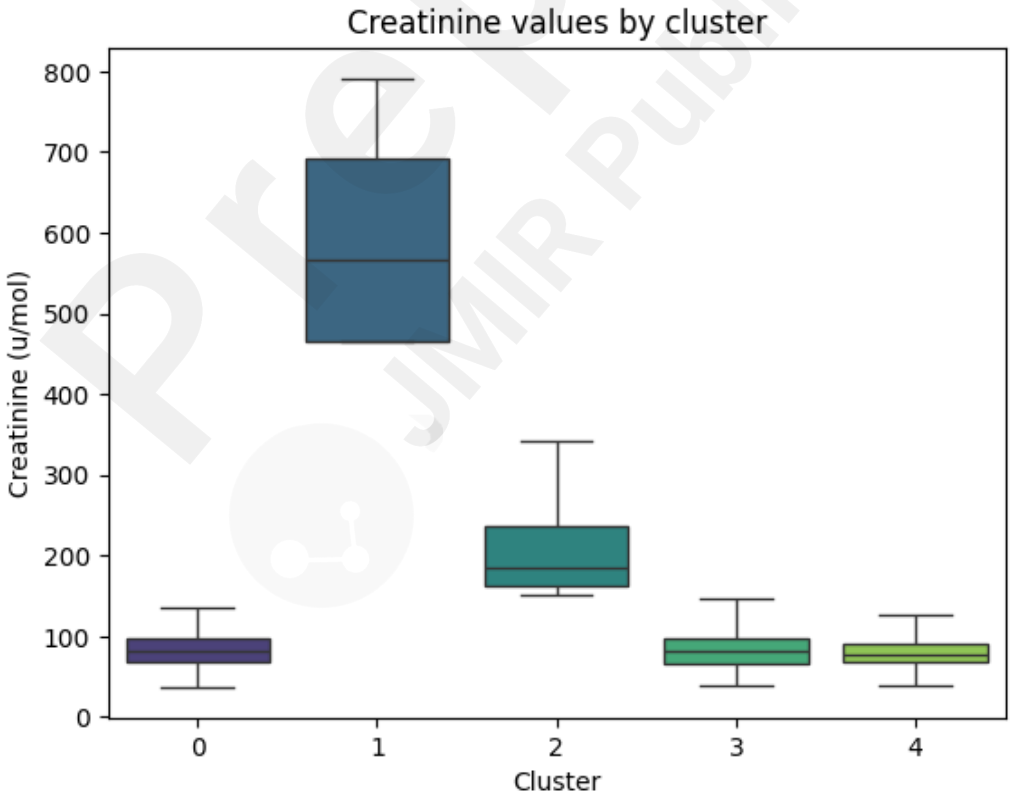

Figure 8: Creatinine value distribution among the 5 clusters identified in DTW Clusters

Running ANOVA (with significance of 0.05) did show that there were creatinine differences between each cluster. Additionally, all extracted ECG features with the exception of P-axis,

T-axis, and PR interval were shown to be statistically significant from cluster to cluster. This indicates that the clusters did measurably separate the ECG time series not just by time series shape but also by the relevant values or sections that would be extracted from the series.

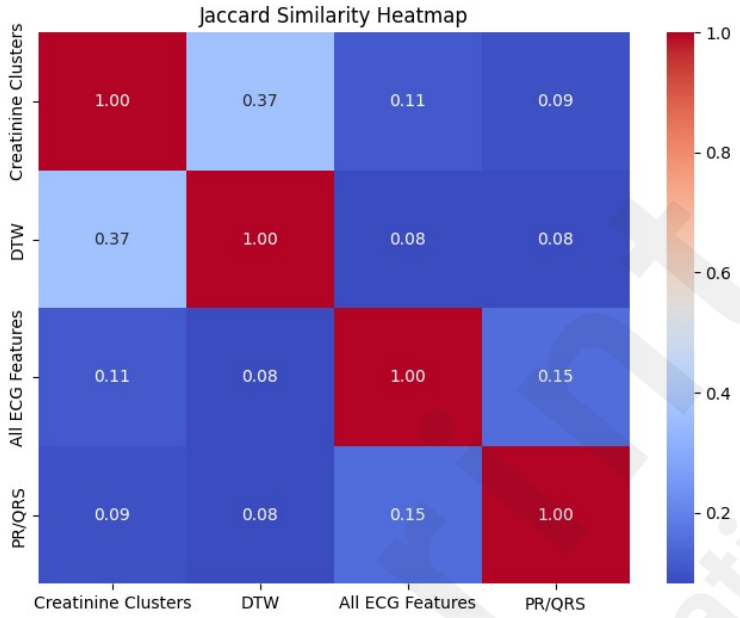

Figure 9: Jaccard score heatmap that compares the clusters' similarities to each other.

From Figure 9, the DTW created clusters are most similar to the creatinine-based clusters. This means it's a better stand-in for CKD enrichment that clustering on solely ECG extracted features.

Discussion

From the results, the PR interval and QRS duration are shown to be the extracted ECG variables most associated with CKD in the HFpEF cohort. This follows the biological rationale as the PR interval and QRS complex are two important features of an ECG signal that capture both time and spatial dynamics of a cardiac cycle. Each aspect of the selected ECG features can provide valuable information about the heart's function. Since the heart pumps blood systemically and into lungs and kidneys, the electric signals may also inform on any altered hemodynamics in the latter organs [28].
The PR interval represents the time it takes for the electrical impulse to travel from the sinoatrial (SA) node, through the atria, to the ventricles. A prolonged PR interval may indicate a delay in the conduction of the electrical impulse, which can be caused by various conditions, and is often suggestive of atrial abnormalities (e.g. atrial volume, strain). The atrial changes can in turn affect subsequent changes in ventricular contraction phase [29].
The QRS complex represents the depolarization of the ventricles which triggers the contraction of the ventricles and the pumping of blood out of the heart into systemic circulation. The duration of the QRS complex is an important indicator of the heart's function and a prolongation may indicate a delay in the conduction of the electrical impulse through the ventricles, which can be caused by various conditions, including bundle branch blocks, ventricular hypertrophy, or myocardial infarction [30,31]. There is evidence to suggest that abnormalities in the PR interval and QRS duration may be associated with an increased risk of kidney disease in patients with HFpEF [29].

To make the connection from heart to the kidney as shown in Figure 1, it is important to note that these two-time intervals reflect the heart's electrical conductance system, and are intricately linked to cardiac relaxation, also known as diastole. During diastole the heart fills with blood after the contraction of the ventricles and this relaxation phase is important for maintaining adequate blood flow to the whole body, a capacity that is often lost in some HFpEF patients.

Despite the supported relationship between PR interval and QRS duration with CKD in HFpEF, the PR-QRS clusters did not demonstrate much similarity with the established creatinine clusters. Additionally, these PR-QRS clusters demonstrated low stability and less pronounced CKD incidence rates among the individual clusters. However, the PR-QRS clusters' Jaccard similarity with the creatinine scores (0.09) and silhouette scores were similar to that of the ECG Feature clusters' Jaccard similarity (0.11) with the creatinine scores and silhouette scores. This indicates that clustering on PR-QRS performs similarly to clustering on all extracted ECG features -- further demonstrating that a relationship between PR interval and QRS duration with CKD in HFpEF. Nevertheless, due to the cluster instability and low Jaccard similarity with the creatinine baseline, it could not be used for informing clinical decisions.

DTW clusters performed much better than the PR-QRS clusters and ECG Feature clusters in terms of Jaccard similarity (0.37) to the established creatinine baseline. Although the cluster groupings were not perfectly equivalent, the similarity demonstrates the potential application of using DTW for ECG clustering. This is intuitively expected due to the DTW being able to fully utilize the entire ECG signal. Previous literature has also supported the clustering capabilities of DTW for ECG and other signal based records.

However, the specific reason for why DTW performed better remains to be seen. Knowing the particular aspects DTW captures that extracted ECG features do not could be used for better understanding of the statistical aspects of DTW application for clustering as well as the cardiorenal relationship between HFpEF and CKD in this case.

Limitations

There were certain limitations to the dataset, most notably with regard to its demographics. As the FinnGen study aggregates data from Finnish biobanks, the population is overwhelmingly Finnish and lacking heterogeneity that may pose a challenge to generalizability to other populations. Certain patients were also overrepresented in the dataset. The average HFpEF patient had 5 ECGs spaced over a year period. However, there were patients who had many ECG records (greater than 5) and patients with only a few ECG records. The patients with many records tended to have greater comorbidities and were thus overrepresented in the dataset. The FinnGen EA3 Heart Failure cohort is also not representative of all heart failure or HFpEF patients. This means that extrapolating this project's results to the wider population may not have as good results. There are disease differences between FinnGen and the external population – the renal and cardiovascular outcome may not perform well.

Additionally, although all data was sourced from the FinnGen EA3 Heart Failure cohort, the cohort itself is comprised of several different biobanks and each biobank provides differing amounts of data. ECG data were only available from the Central Finland Biobank. This meant that, while some patients had characteristics that indicated HFpEF, they could not be included in this study since they were lacking ECG data. This data limitation introduces bias as it means all individual data is effectively from the Central Finland Biobank.

HFpEF itself is also difficult to diagnosis. There was a lack of diagnosis codes in the FinnGen EA3 Heart Failure cohort. Thus, although LVEF and NT-proBNP values were used to determine individuals that have HFpEF indications, it is difficult to say if such individuals are definitively HFpEF patients. However, although this selected cohort may not be purely composed of clinically diagnosed HFpEF patients, it is almost guaranteed that it is enriched for HFpEF patients. Furthermore, as the biological rationale behind the hypothesis is on the cardiorenal associations between the heart and kidneys, it is the specific heart features (i.e. hypercontractility and failure) that are most relevant rather than a clinical diagnosis.

In addition, DTW also has its own limitations. Although it does consider the entire ECG signal, it reduces it down to a singular similarity metric (i.e. distance) that may be reductive. Additionally, it is very computationally intensive and sensitive to noise. Extracted ECG values are not as sensitive to noise.

The main challenge with DTW was the time needed for calculations -- it took a long time for every calculation. Since distance needed to be calculated for every possible time series pair (of which there were 14000 due to an average of 5 ECGs per patient), this was very time consuming. Since all analysis took place within the FinnGen sandbox which is a closed virtual machine environment, not all packages were available. This included the conventional packages for DTW calculations. This was further parallelized using python's multiprocessing library for efficiency's sake.

Future Directions

Applying ECG clustering with DTW to other disease areas for similar cluster enrichment analysis may be fruitful. Previous literature has demonstrated the capabilities of ECG for risk prediction in both cardiovascular and non-cardiovascular disease areas. Analyzing the differences in cluster enrichment analysis with DTW and classic supervised risk prediction approaches may be informative.

Further work could also segment the ECG time signals. In doing so, each area could be examined for their contribution to the DTW determined signal similarity or distance. This way, the parts of the ECG that most affect DTW distance could be identified and determined. However, this method would be very computationally intensive – even more so than the current approach which requires calculations for every pairwise ECG combination. Additionally, the FinnGen sandbox that houses the EA3 Heart Failure study only allows select python packages to be installed and used (e.g. the most popular and well known ones such as pandas, numpy, matplotlib, scikit-learn, and more). DTW related packages such as fastdtw, dtaidistance, or tslearn are not available on the server and must be manually coded and parallelized. This work would also need to be done for any signal segmentation DTW analysis.

Other future work involves incorporating DTW distance as a representation into autoencoders. Previous literature in both ECG and non-ECG areas has shown autoencoders to be accurate for disease trajectory and risk assessment [32]. Incorporating not just the extracted ECG signals into autoencoders but perhaps also a DTW score can be helpful.

Additionally, this study did not consider all comorbidities that are known to be associated with HFpEF [1] nor did it account for associated changes due to medications use in the selected cohort for example blood pressure control. As such, the study has limited its scope to cardiac specific criteria and specific analytes e.g. creatinine in its methodology to understand the direct cardiorenal association. In the future, we may want to understand the potential synergies and constraints derived by adding more features, and that may improve the accuracy of the prediction. In particular, we may want to evaluate the combinatorial effect of underlying physiology, medication, pre-existing

diseases, urinary and blood based metabolic and protein biomarkers, and genetics that may interact with each other and our selected features. While lack of various associated clinical data may be a limitation of this study, we propose that our approach minimizes non cardiac effects that may often mask the true association between organs e.g. changes in blood pressure or pulmonary changes that may also be seen in HFpEF that have shown as a phenogroup in earlier studies [18], do not stand in conflict with our methodology. As we validate our study using other public dataset, e.g. UKB, we would consider expanding the scope of the analysis.

Conclusion

From the results, the PR interval and QRS duration are shown to be the extracted ECG variables most associated with CKD in the HFpEF cohort. This follows the biological rationale as the PR interval and QRS complex are two important features of an ECG signal that capture both time and spatial dynamics of a cardiac cycle. DTW application for ECG clustering would also be fruitful to explore.

Ethical Considerations

The real-world electronic health data used from the FinnGen database provided for analysis were already anonymized by FinnGen.

The FinnGen study is approved by Finnish Institute for Health and Welfare (permit numbers: THL/2031/6.02.00/2017, THL/1101/5.05.00/2017, THL/341/6.02.00/2018, THL/2222/6.02.00/2018, THL/283/6.02.00/2019, THL/1721/5.05.00/2019 and THL/1524/5.05.00/2020), Digital and population data service agency (permit numbers: VRK43431/2017-3, VRK/6909/2018-3, VRK/4415/2019-3), the Social Insurance Institution (permit numbers: KELA 58/522/2017, KELA 131/522/2018, KELA 70/522/2019, KELA 98/522/2019, KELA 134/522/2019, KELA 138/522/2019, KELA 2/522/2020, KELA 16/522/2020), Findata permit numbers THL/2364/14.02/2020, THL/4055/14.06.00/2020, THL/3433/14.06.00/2020, THL/4432/14.06/2020, THL/5189/14.06/2020, THL/5894/14.06.00/2020, THL/6619/14.06.00/2020, THL/209/14.06.00/2021, THL/688/14.06.00/2021, THL/1284/14.06.00/2021, THL/1965/14.06.00/2021, THL/5546/14.02.00/2020, THL/2658/14.06.00/2021, THL/4235/14.06.00/2021, Statistics Finland (permit numbers: TK-53-1041-17 and TK/143/07.03.00/2020 (earlier TK-53-90-20) TK/1735/07.03.00/2021, TK/3112/07.03.00/2021) and Finnish Registry for Kidney Diseases permission/extract from the meeting minutes on 4th July 2019. The Biobank Access Decisions for FinnGen samples and data utilized in FinnGen Data Freeze 12 include: THL Biobank BB2017_55, BB2017_111, BB2018_19, BB_2018_34, BB_2018_67, BB2018_71, BB2019_7, BB2019_8, BB2019_26, BB2020_1, BB2021_65, Finnish Red Cross Blood Service Biobank 7.12.2017, Helsinki Biobank HUS/359/2017, HUS/248/2020, HUS/430/2021 28, 29, HUS/150/2022 12, 13, 14, 15, 16, 17, 18, 23, 58, 59, HUS/128/2023 18, Auria Biobank AB17-5154 and amendment 1 (August 17 2020) and amendments BB_2021-0140, BB_2021-0156 (August 26 2021, Feb 2 2022), BB_2021-0169, BB_2021-0179, BB_2021-0161, AB20-5926 and amendment 1 (April 23 2020) and its modifications (Sep 22 2021), BB_2022-0262, BB_2022-0256, Biobank Borealis of Northern Finland_2017_1013, 2021_5010, 2021_5010 Amendment, 2021_5018, 2021_5018 Amendment, 2021_5015, 2021_5015 Amendment, 2021_5015 Amendment_2, 2021_5023, 2021_5023 Amendment, 2021_5023 Amendment_2, 2021_5017, 2021_5017 Amendment, 2022_6001,

2022_6001 Amendment, 2022_6006 Amendment, 2022_6006 Amendment, 2022_6006 Amendment_2, BB22-0067, 2022_0262, 2022_0262 Amendment, Biobank of Eastern Finland 1186/2018 and amendment 22/2020, 53/2021, 13/2022, 14/2022, 15/2022, 27/2022, 28/2022, 29/2022, 33/2022, 35/2022, 36/2022, 37/2022, 39/2022, 7/2023, 32/2023, 33/2023, 34/2023, 35/2023, 36/2023, 37/2023, 38/2023, 39/2023, 40/2023, 41/2023, Finnish Clinical Biobank Tampere MH0004 and amendments (21.02.2020 and 06.10.2020), BB2021-0140 8/2021, 9/2021, 9/2022, 10/2022, 12/2022, 13/2022, 20/2022, 21/2022, 22/2022, 23/2022, 28/2022, 29/2022, 30/2022, 31/2022, 32/2022, 38/2022, 40/2022, 42/2022, 1/2023, Central Finland Biobank 1-2017, BB_2021-0161, BB_2021-0169, BB_2021-0179, BB_2021-0170, BB_2022-0256, BB_2022-0262, BB22-0067, Decision allowing to continue data processing until 31st Aug 2024 for projects: BB_2021-0179, BB22-0067,BB_2022-0262, BB_2021-0170, BB_2021-0164, BB_2021-0161, and BB_2021-0169, and Terveystalo Biobank STB 2018001 and amendment 25th Aug 2020, Finnish Hematological Registry and Clinical Biobank decision 18th June 2021, Arctic biobank P0844: ARC_2021_1001.

Author Contributions

SF and ZY drove the study conceptualization and design. SZ and ZY executed the quantitative analysis, processed the experimental data, performed the statistical analysis, and created the figures. BA provided insight on data informatics and medical writing. JL and MV provided support through FinnGen. The manuscript was drafted, revised, and edited by BA, SF, SZ, ZY.

Financial disclosure

This research was funded by Pfizer, Inc. The data was publicly made available by FinnGen.

Acknowledgments

We would like to thank Sabrina Hsueh, Asa Hedman, Craig Hyde, the FinnGen team for their careful review of the manuscript and for their support for this study conduct. We would also like to acknowledge the participants and investigators of the FinnGen study.

Data Availability

Based on National and European regulations (GDPR) access to individual-level sensitive health data must be approved by national authorities for specific research projects and for specifically listed and approved researchers. The health data described here was generated and provided by the National Health Register Authorities (Finnish Institute of Health and Welfare, Statistics Finland, KELA, Digital and Population Data Services Agency) and approved, either by the individual authorities or by the Finnish Data Authority, Findata, for use in the FinnGen project. Therefore, we, the authors of this paper, are not in a position to grant access to individual-level data to others. However, any researcher can apply for the health register data from the Finnish Data Authority Findata (https://findata.fi/en/permits/) and for individual-level genotype data from Finnish biobanks via the

Fingenious portal (https://site.fingenious.fi/en/) hosted by the Finnish Biobank Cooperative FINBB (https://finbb.fi/en/).

Conflicts of Interest

S.F., Z.Y and B.A are employees and shareholders of Pfizer, Inc. S Z. is an intern at Pfizer Inc. at the time of the work.

Multimedia Appendix

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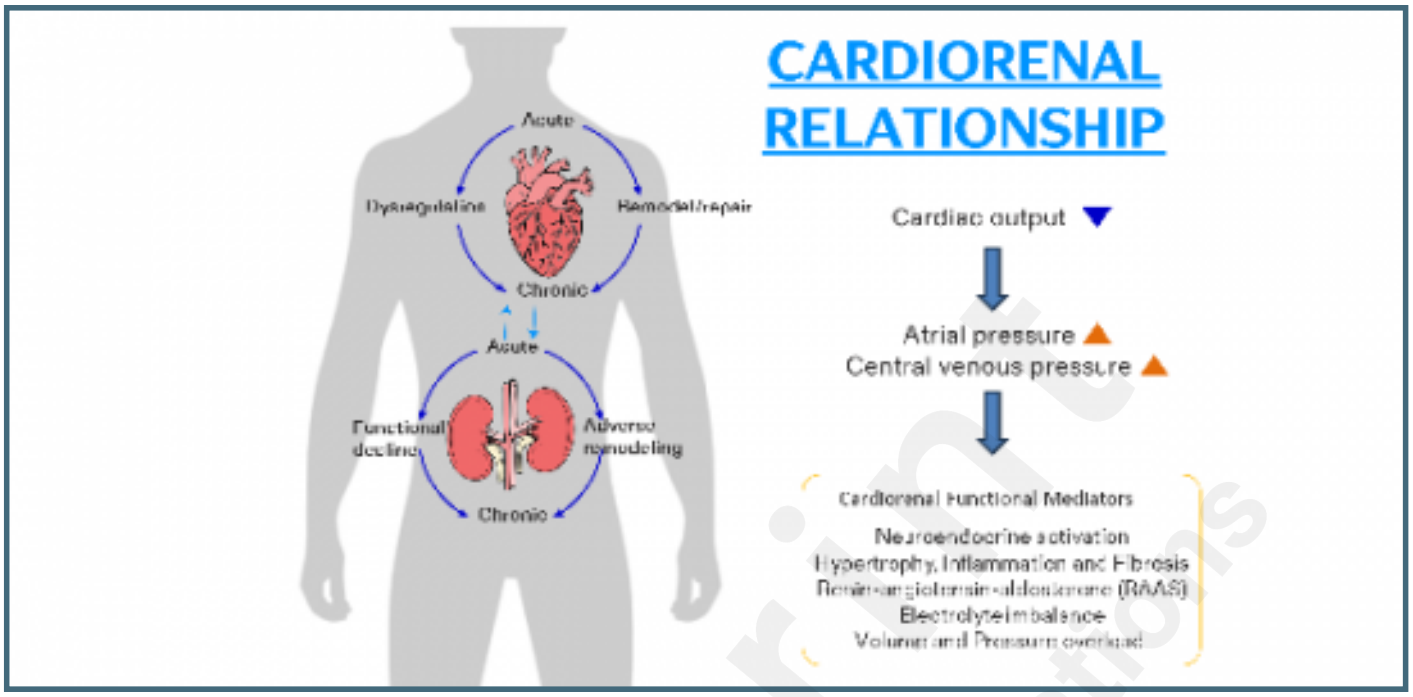
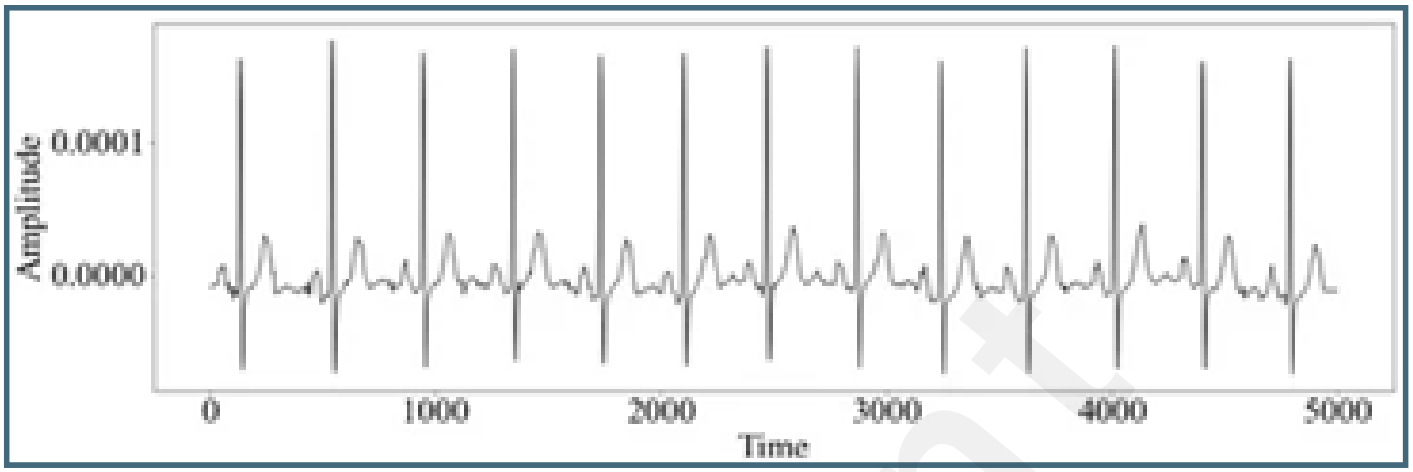
Supplementary Files

Figures

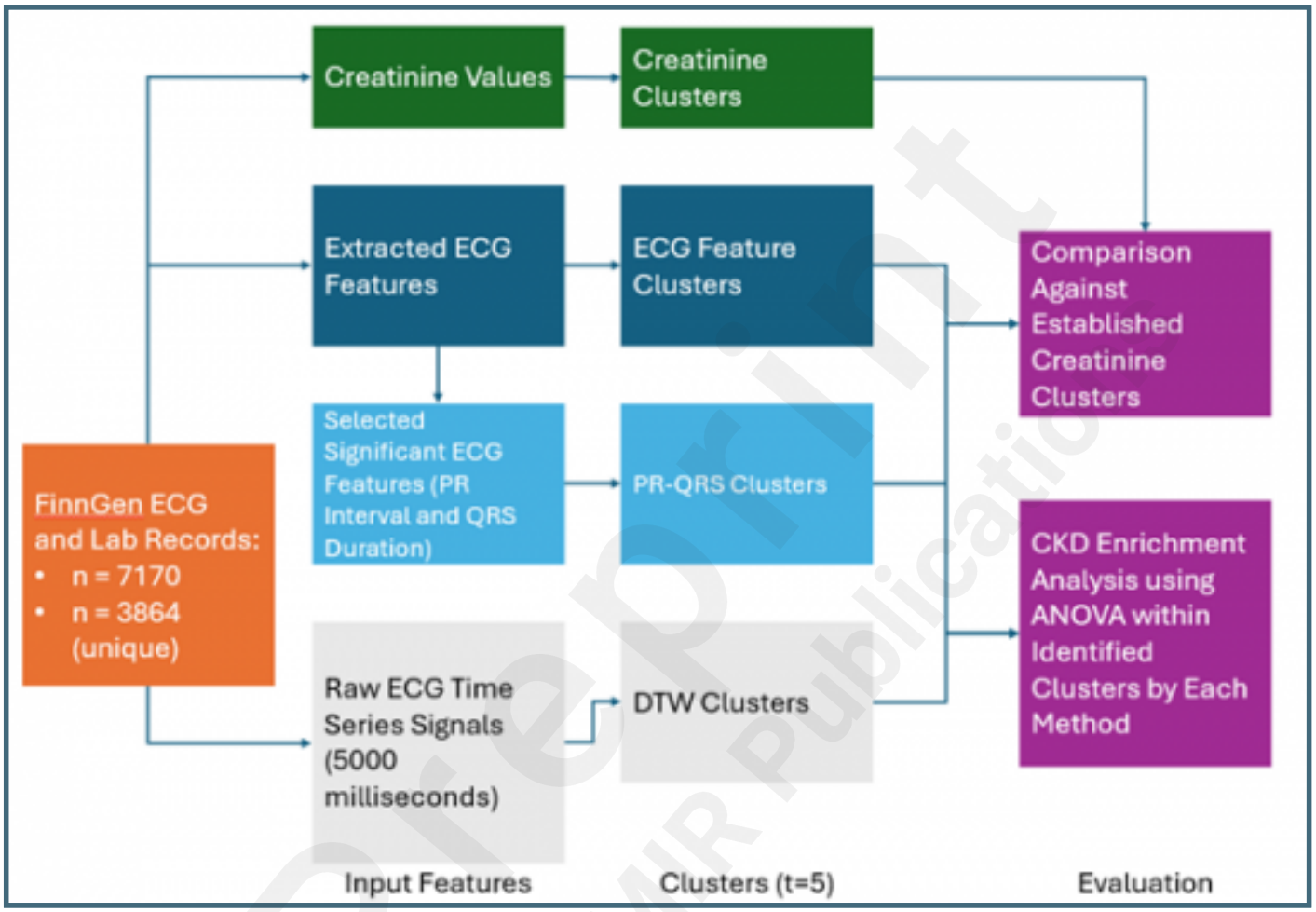
Illustration of the cardiorenal relationship and functional mediators.



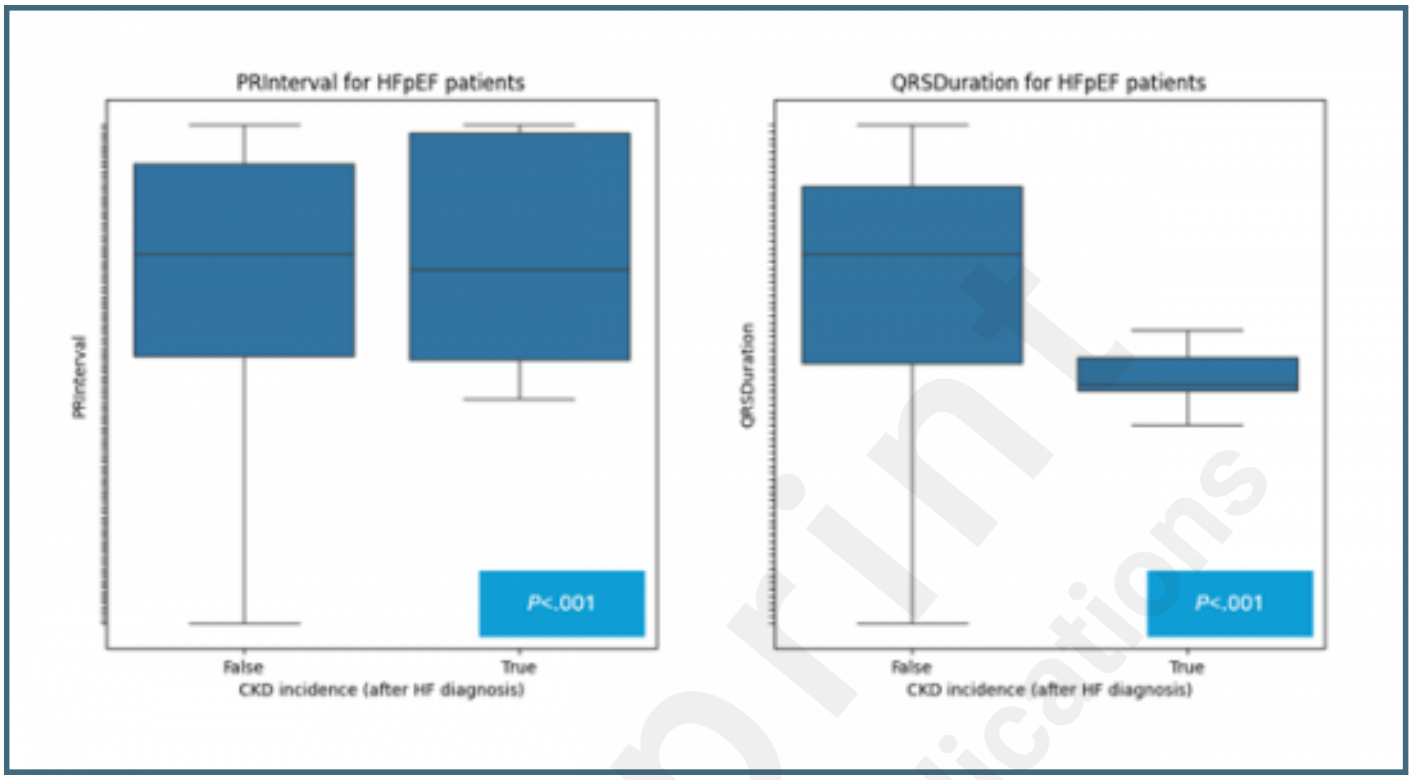
A sample Lead II ECG wave[25].



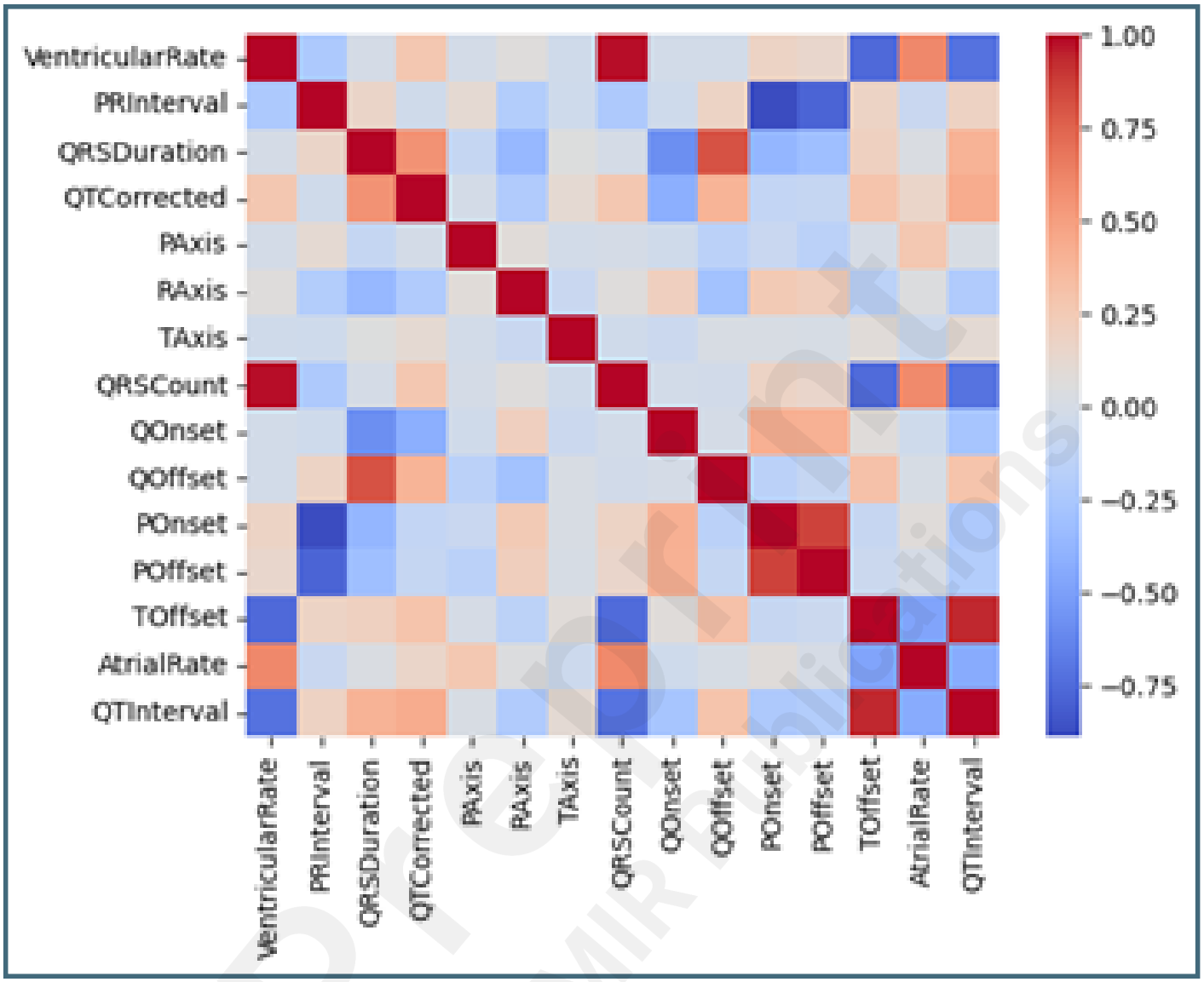
An illustration of the methodology workflow. FinnGen ECG and lab records are used to create different sets of clusters: Creatinine clusters (hierarchical clusters based off creatinine labs to be used as a baseline indication for CKD), ECG feature clusters (clusters created using all extracted ECG features), PR-QRS clusters (clusters created using top variables determined to be significant in predicting CKD in HFpEF), and DTW clusters (clusters created using DTW on the raw ECG time series). For each set of clusters, 5 groups were formed.



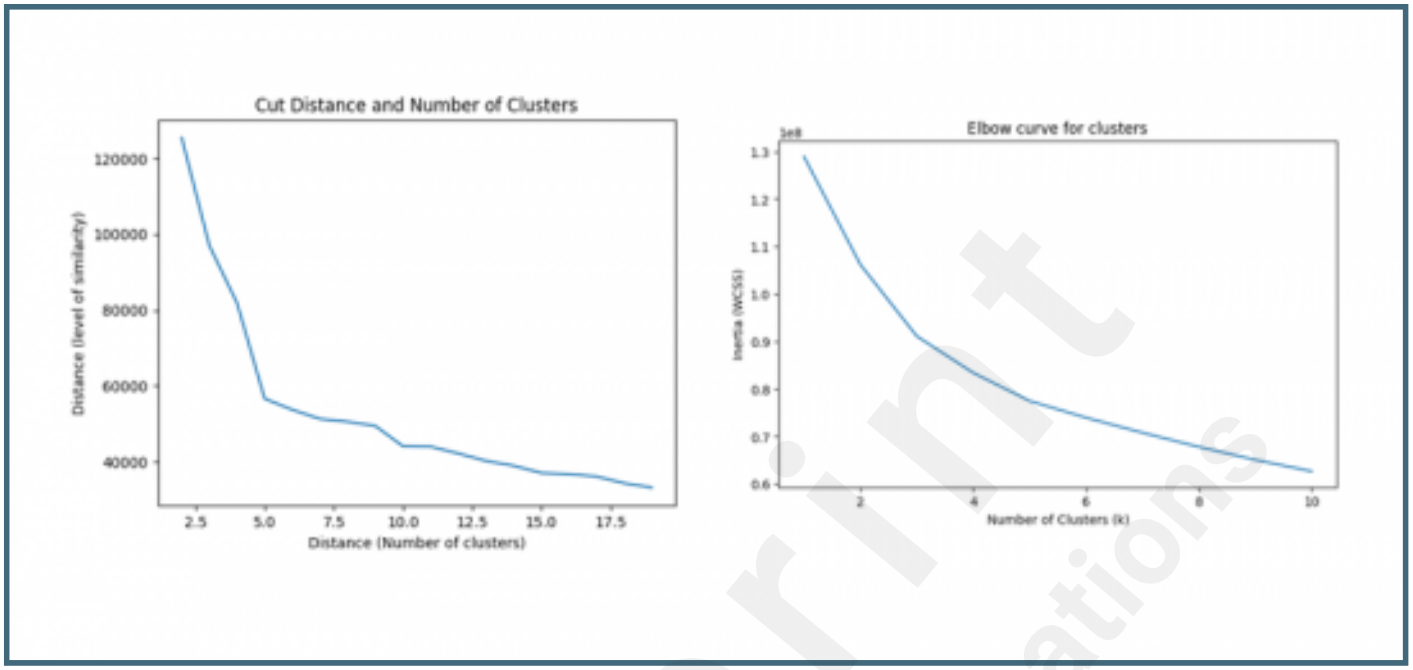
Distribution of significant extracted ECG values (QRS Duration and PR Interval) between CKD positive and negative patients.



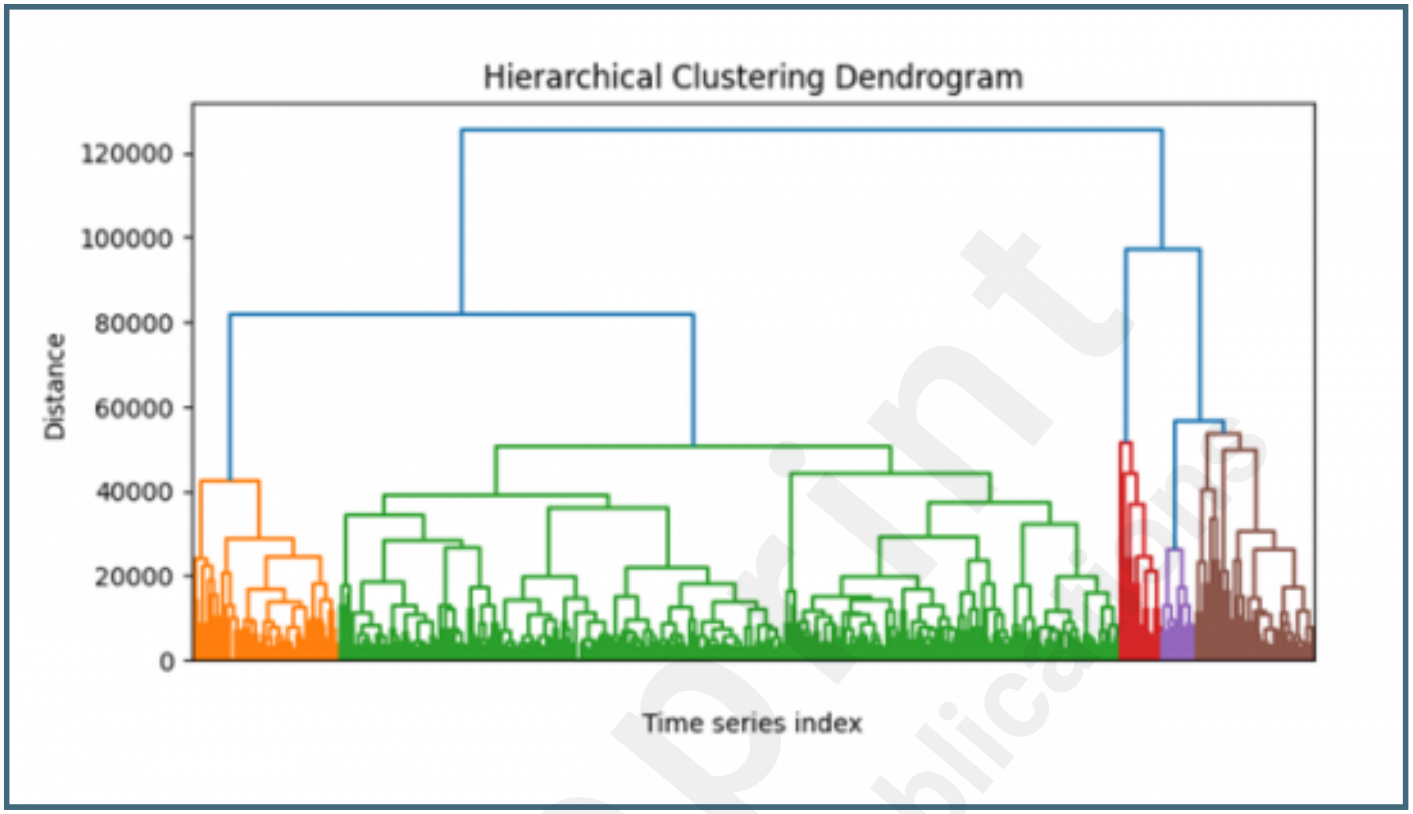
A heatmap showing the correlation between extracted ECG features.



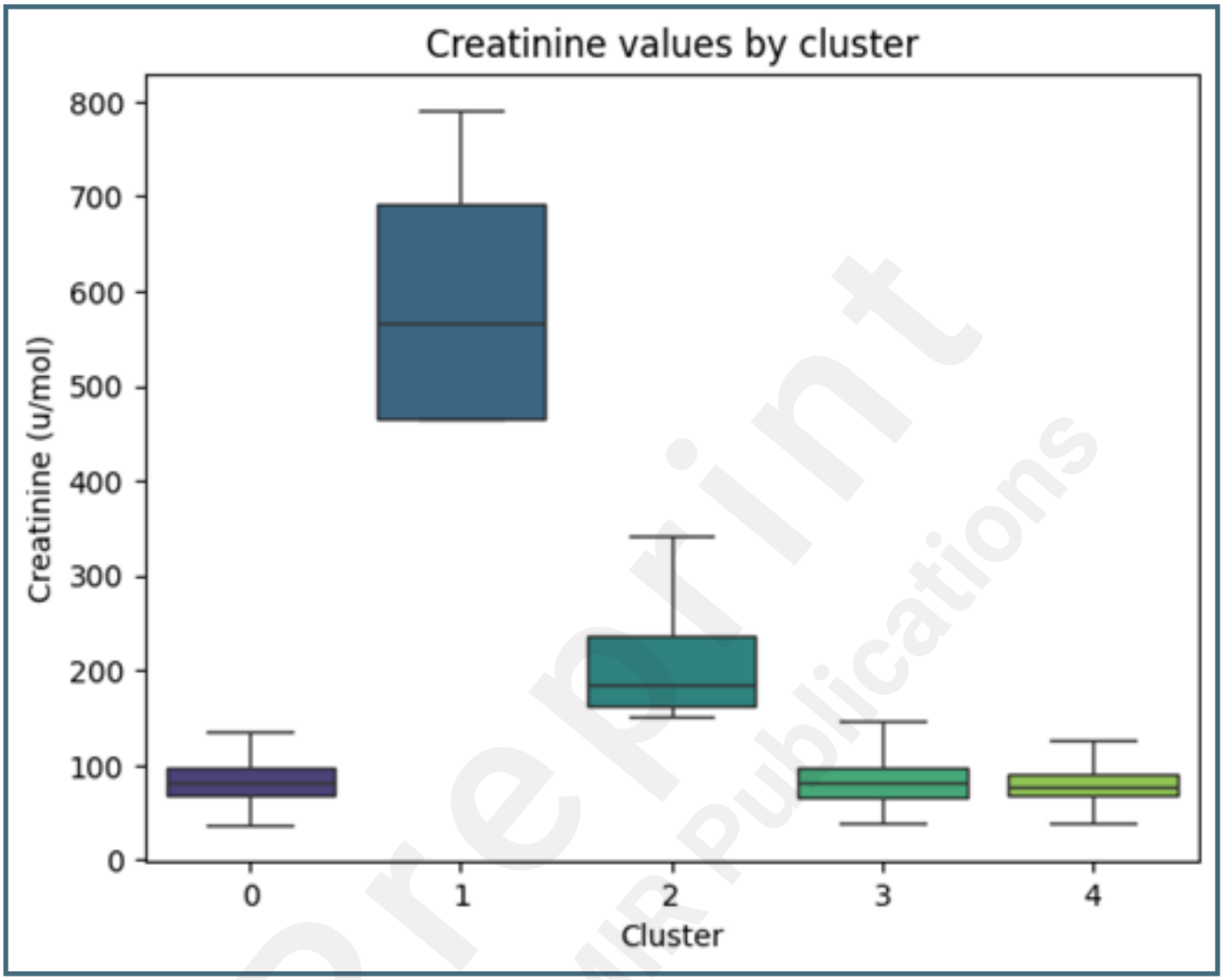
Elbow curves for extracted feature and DTW hierarchical clustering. This was used to determine the optimal number of clusters (t=5). The number of clusters was determined using these elbow charts and by seeing where the reduction in inertia or cut threshold has diminishing returns.



Hierarchical clustering on the validation set. We can see that approximately five clusters form which match up to the number of clusters estimated using the elbow method on the extracted ECG values. Due to the number of time series that were clustered, there were too many labels to list individually.



Creatinine value distribution among the 5 clusters identified in DTW Clusters.



Jaccard score heatmap that compares the clusters' similarities to each other.