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Investigation of potential biomarkers in prediction of acute myocardial infarction via explainable artificial intelligence

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Abstract

Remodeling of the left ventricle (LV) after myocardial infarction (MI) is a process of infarct enlargement. Despite the relevance of the inflammatory response and healing process in LV remodeling after MI, the mechanisms that begin and govern these processes remain unknown. Based on the important information highlighted in different studies, the current research aims to investigate potential biomarkers for left ventricular remodeling after acute MI based on the interpretation of the explainable artificial intelligence (XAI). The project research from which the public dataset was obtained was designed in an experimental type. A cohort study involving 66 patients with coronary heart disease and 34 healthy community controls provided the platelet samples for the current research, which used available omics data on those samples. For discovering significant mechanistic connections between metabolites and glycans, the metabolomics and glycomics datasets were analyzed using biostatistics/metabolomics and explainable artificial intelligence techniques. Metabolomics data of 100 patients (AMI=66; Control=34) including 75 males and 25 females were evaluated in this study. As a result of experimental omics analyses, 102 metabolite levels of the patients were obtained. When FC values were examined, creatinine and dl-pipecolic acid levels were 0.50 and 0.55-fold down-regulated and glutamine, myoinositol, and cytosine levels were 1.34, 1.33, and 1.53-fold up-regulated in the AMI group compared to the control group. Findings of metabolomics data and XAI analyses revealed that five lipid metabolites may be used as potential predictors of AMI.

Keywords: Acute myocardial infarction, explainable artificial intelligence, biomarkers

Introduction

During myocardial infarction (AMI), the left ventricle (LV) remodels as a result of infarct enlargement. Following the event, there is increasing LV dilatation and non-infarct hypertrophy. Despite the relevance of the inflammatory system and process of healing in LV remodeling after MI, the mechanisms that begin and govern these processes remain unknown. LV remodeling after MI leads to significant clinical consequences in the long run. Poor infarct healing is a major factor in infarct size, wall stress, and infarct growth [1,2]. After a MI, an appropriately timed inflammatory reaction results in the formation of a tensile-strengthy scar and an appropriate infarct healing process, which stops the infarct from growing. Many clinical and experimental investigations have been conducted to investigate the function and regulatory mechanism of inflammation as a potential therapeutic target for post-infarction LV remodeling. Many biological mechanisms have been proposed for left ventricular remodeling. Local ischemia and myocardial cell death, oxidative stress and inflammatory reactions in damaged myocardium [3], cardio-depressive reactions due to reactive oxygen species and inflammatory cytokines [4,5], changes in the extracellular

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matrix following activation of matrix metalloproteinases [6,7], structural changes of the myocardium in response to mechanical stress, production of collagen and myocardial fibrosis [8] are the main mechanisms proposed. These reactive mechanisms are interconnected and develop from acute responses to chronic alterations. LV remodeling causes related dysfunction and dilatation. The result might be one of the most important predictors of a patient's prognosis after myocardial infarction.

The function of biomarkers in LV remodeling diagnosis, prediction, stratification, and prevention has not been adequately addressed. Many novel biomarkers, including heart fatty acid-binding protein (hFABP), ischemia-modified albumin (IMA), and sarcomeric cardiac myosin-binding protein C, have recently been identified (cMyC) [9,10]. Machine learning has been employed for discovering possible metabolomics biomarkers in recent years. A new technique for AMI detection was provided by combining metabolomics and machine learning algorithms and multi layer perceptron (MLP) model based on seven molecular indicators performed well in both AMI rats and autopsy-established blood samples [11].

Artificial intelligence (AI) is a key component of many clinical decision support systems, allowing procedures to infer judgements computationally similar to human thinking processes [12]. These strategies are based on medical knowledge explicitly encoded with rules or automatically derived from medical data via machine learning. People should continue to be at the center of therapy, and they should be empowered to make their own choices about their health in collaboration with clinicians, according to explainable AI (XAI) [13]. Based on the important information highlighted in different studies, the current research aims to investigate potential biomarkers for left ventricular remodeling after acute MI based on the interpretation of the XAI.

Material and Methods

Study Design and Data

The project research from which the public dataset was obtained was designed in an experimental type. Sixty six patients with coronary heart disease and 34 healthy community controls composed the cohort used in the current research, which used available omics data on platelet samples. For discovering significant mechanistic connections between metabolites and glycans, the metabolomics and glycomics datasets were analyzed using biostatistics/metabolomics and explainable artificial intelligence techniques. The associated information can be found on the Metabolomics Workbench website at https://www.metabolomicsworkbench.org, where it has been given Project ID (PR001202). The Project DOI: (10.21228/M8BD7S) [14] allows immediate access to the data. The minimum sample size for the research was determined to be 30 patients, 15 in each group, using the MetSizeR program, the FDR value of 0.05, and probabilistic principal component analysis (PPCA) [15]. The current work encapsulates a total of 100 individuals (66 in patient and 34 in control groups).

The inclusion criteria in the current study were as follows:

a. ST-elevation myocardial infarction (STEMI) identified in a hospital environment; ischemic chest discomfort or angina-like symptoms (acute onset dyspnea) in the past; Q waves are present; cardiac enzymes (cardiac troponins, cTn) value exceeding the 99th percentile upper reference limit (in ng/L or pg/mL) or clinically diagnosed non-ST-elevation myocardial infarction (NSTEMI); electrocardiogram (ECG) alterations deviating from normal increase and decrease; cardiac troponins (cTn) value exceeding the 99th percentile upper reference limit (in mm/L (CKMB)),

b. Angiographic results of one or more coronary arteries that are more than 50% blocked,

c. Age >21 years and 85 years

d. Ability to follow protocol standards and give written, informed consent.

Following are the study's selection criteria:

a. Patients unable or unwilling to provide informed permission for the research,

b. Individuals with significant renal impairment [eGFR less than 15 ml/min/m2],

c. . Patients who suffer from serious liver damage,

d. Anaemia < 8 g/dl (men) and 7 g/dl (women),

e. Cardiogenic shock unresponsive to inotrope withdrawal or intra-aortic balloon pump (IABP),

f. Significant valvular heart disease, including mild to severe mitral stenosis (MS), mitral regurgitation (MR), aortic stenosis (AS), aortic regurgitation (AR), and tricuspid regurgitation (TR),

g. A cancer history was discovered within the preceding 12 months.

h. Individuals who cannot be followed up on (non-residents).

Before collecting samples for this study, no therapy or intervention was administered to the patients. Both coronary heart disease patients and participants in good condition had their platelets sampled. The preparation of the samples was necessary in order to carry out the simultaneous extraction of metabolites and glycans. Mass spectrometry was employed in the analytical experiments using Thermo Dionex Ultimate 3000 chromatography system. Detailed information can be accessed from the relevant research [14].

Metabolomics Data Analysis

Univariate fold change (FC) analyses were performed to find potential biomarkers [16]. The Volcano plot was drawn to represent the FC analysis results graphically. In the Volcano graph, the comparison direction was set to AMI/Control. P-values were modified to account for the false detection rate (FDR). To identify metabolites with significantly varying levels in the AMI

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and control groups, the threshold for $p < 0.05$ and 1 for FC were set, thereby identifying potential biomarkers. Metabolites with an FC value below 1 were down-regulated, and metabolites with an FC value above 1 were up-regulated. Bioinformatics analyses were performed using the MetaboAnalyst version 5.0 program to identify the metabolites that varied between the AMI and control groups.

Biostatistical Data Analysis

Quantitative data were summarized as the interquartile range (IQR) with the median, and quantitative data were reported as the frequency with percentage. The qualitative factors' normal distribution was examined using the Kolmogorov-Smirnov test of normality. Since the quantitative variables did not exhibit normal distribution, the acute myocardial infarction (AMI) and control groups were compared using the Mann-Whitney U test. p-values less than 0.05 are regarded as significant. To describe statistical differences, American Psychological Association (APA) 6.0 style was used [17]. Software from IBM SPSS Statistics for Windows, version 28.0 (New York; USA), was used for all statistical analyses.

Model Development

A predictive model was constructed with the Gradient Boosted Trees (GBT) algorithm using differentially expressed metabolites to distinguish AMI patients from healthy controls. The concept that boosting can be seen as an optimization technique on a suitable cost function gave rise to the GBT algorithm. The problem of the differentiable loss function is solved using it. GBT is an ensemble method that performs regression or classification tasks by combining the outputs from individual trees [18]. For the modeling stage, the relevant data was divided as 80% for the training/discovery set and 20% for a testing/validation set, and this process was repeated 100 times. The mean values for 100 repetitions were then taken. The model's performance was assessed using the accuracy, F1-score, precision, recall, and area under the ROC curve (AUC) parameters. The Local Interpretable Model-Agnostic Explanations (LIME) method was used to obtain patient-specific model annotations in order to improve the model's interpretability. For the reliability of the results of AI systems, it is essential that the models are explainable to the users/researchers. LIME is an XAI method that provides the "why" of predictions or recommendations generated by AI [19].

Results

Metabolomics data of 100 patients (AMI=66; Control=34) including 75 males and 25 females were evaluated in this study. As a result of experimental omics analyses, levels of 102 metabolites were obtained. Forty (39.21%) of the metabolites were from the organic acids class, and 25 (24.51%) were from the nucleic acids class.

The results of metabolomics data analysis summarize the first five findings related to the adjusted p values in Table 1. As shown in Table 1, two metabolites (names:Creatinine and DL-Pipecolic acid) were down-regulated, and three other metabolites (glutamine, Myo-inositol, and Cytosine) were up-regulated. When FC values were examined, creatinine and DL-Pipecolic acid levels were 0.50 and 0.55-fold down-regulated in the AMI group compared to the control group, respectively. In addition, glutamine, Myo-inositol, and cytosine levels were 1.34, 1.33, and 1.53-fold up-regulated in the AMI group compared to the control group, respectively.

Table 1. Analytical results of metabolomics data analysis

Metabolite Name	FC	Log_2 FC	Adj. p-value	$-Log^{10}$ (p-value)	Diff. Expressed
Creatinine	0.50	-1.00	0.036	1.44	Down
glutamine	1.34	0.42	0.036	1.44	Up
myo-inositol	1.33	0.41	0.038	1.42	Up
DL-Pipecolic acid	0.55	-0.87	0.042	1.38	Down
cytosine	1.53	0.62	0.043	1.37	Up

FC: fold change (FC)

For the chosen metabolites, descriptive data are shown in Table 2. Table 2 displays substantial variations in creatinine, glutamine, myo-inositol, and DL-pipecolic acid metabolites between the AMI and control groups ($p<0.001$). The amounts of pipecolic acid in the AMI group were significantly higher than those in the control group for creatinine, glutamine, myo-inositol, and DL. Nevertheless, there was no discernible difference in the levels of cytosine between the groups ($p>0.05$).

Table 2. The results of biostatistical data analysis

Metabolite*	Group		p-value
	Control	AMI	
Creatinine	814344.50 (358762.79)	1373402.12 (521220.39)	<0.001
glutamine	4229789.63 (1461859.53)	5712733.27 (2365103.87)	<0.001
myo-inositol	425054.92 (113461.45)	560025.50 (277390.76)	<0.001
DL-Pipecolic acid	8770575.65a (2910773.07)	12318795.10 (4234629.41)	<0.001
cytosine	186965.38 (293382.80)	143238.57 (325413.37)	0.128

*: Metabolites are summarized as 'median (interquartile range)'.
AMI: acute myocardial infarction

Figure 1 shows the volcano plot that was used to show the various metabolites that were expressed differently. On the x-axis, the volcano plot plotted against the fold change at the base of Log2 indicates the importance of metabolites and differentially expressed metabolites.

Table 3 represents the performance criteria for the selected metabolites with the GBT model. According to Table 3, the Accuracy, F1-score, Precision, Recall, and AUC values obtained with the model created to predict AMI patients were 0.90, 0.90, 0.90, 0.90, and 0.92, respectively.

Table 3. Performance criteria for the GBT model

Metrics	Value
Accuracy	0.90
F1-score	0.90
Precision	0.90
Recall	0.90
AUC	0.92

AUC: area under the ROC curve GBT: gradient boosted trees

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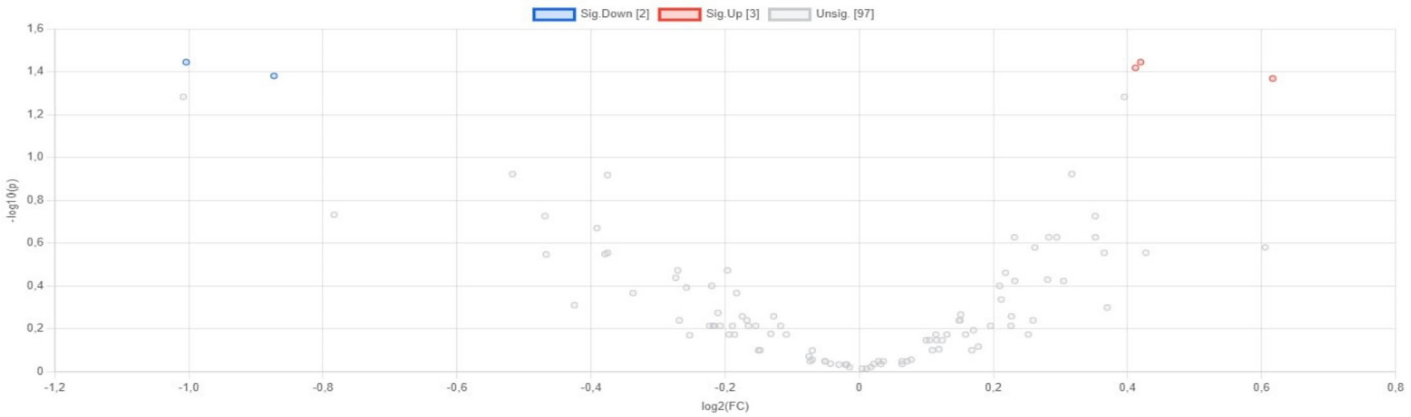

Figure 1. Volcano Plot

Figure 2 contains LIME descriptions for a patient predicted as a true positive (AMI). According to Figure 3, the reason why this patient was correctly predicted was that Creatinine >1456427.47, cytosine<=861.67, DL-Pipecolic acid>13440645.66, Myo-inositol>665921.62 and glutamine>6513473.58 were at the specified levels. The GBT model differentiated the patient under investigation with 100% accuracy.

The metabolites for AMI and the importance coefficients of these metabolites are given in Table 4. According to the results of the research, the first three metabolites contributing the most to AMI are creatinine (38.3%), Cytosine (24.1%) and DL-Pipecolic acid (23.1%), respectively. The LIME model showed that these metabolites within the specified ranges could be a marker of AMI.

Figure 3 contains LIME descriptions for a patient predicted as true negative (control). The related patient was predicted as true negative because Creatinine<=903583.92, Myo-inositol<=419356.02, 4120393.08<glutamine<=5157162.38, DL-Pipecolic acid<=8653138.81 and 861.67<cytosine<= 164169.71 at the indicated levels. The GBT model predicted this person to be healthy with 100% accuracy.

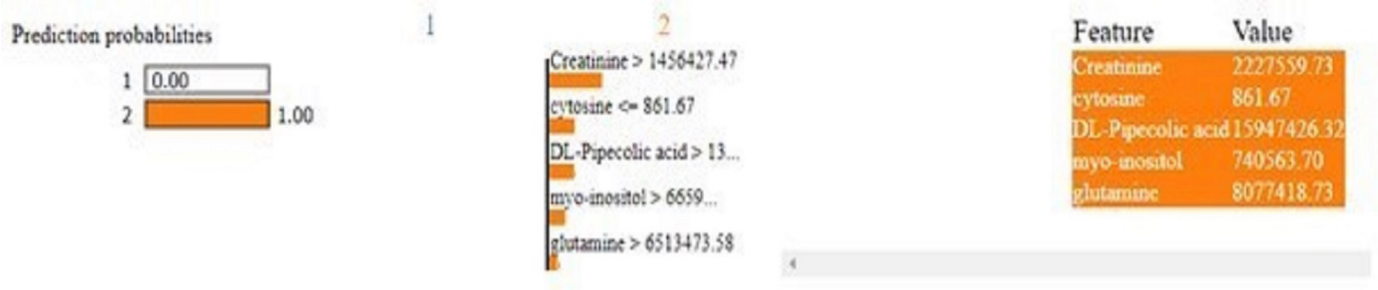

Figure 2. LIME annotations of the prediction result for a patient that the model predicts as true positive (AMI) (1: Control, 2: AMI)

Figure 3. LIME annotations of the prediction result for a patient that the model predicts as true negative (Control) (1: Control, 2: AMI)

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Table 4. The importance of the metabolites for the AMI group

Metabolite level	Importance coefficient
Creatinine > 1456427.47	0.383
cytosine <= 861.67	0.241
DL-Pipecolic acid > 13440645.66	0.231
myo-inositol > 665921.62	0.093
glutamine > 6513473.58	0.052

AMI: acute myocardial infarction

The metabolites for the healthy control group and the importance coefficients of these metabolites are given in Table 5. According to Table 5, the most significant contribution to the model's prediction was creatinine based on the result of LIME. When considered collectively, creatinine (57.9%), myo-inositol (13.1%), and glutamine (11.6%) were the first three metabolites that made the most significant contribution to distinguishing the healthy control group, respectively. The LIME model showed that these metabolites within the specified ranges could be a marker of non-AMI (control).

Table 5. The importance of the metabolites for the healthy control group

Metabolite level	Importance coefficient
Creatinine <= 903583.92	0.579
myo-inositol <= 419356.02	0.132
4120393.08 < glutamine <= 5157162.38	0.116
DL-Pipecolic acid <= 8653138.81	0.098
861.67 < cytosine <= 164169.71	0.075

Discussion

FBased on the interpretations of the XAI, the current research looked into potential biomarkers for left ventricular remodeling following acute MI. XAI can help maintain patients at the center of care and give them the freedom to be informed about independent health decisions while working with professionals [20]. In recent years, a number of diverse methods have been suggested for use in various medical applications, according to a review article [21].

In the first stage of this study, metabolomic and biostatistical data analyzes were applied to the examined public data. Based on the findings of metabolomics data analysis of 102 metabolites, differentially expressed metabolites were creatinine, glutamine, myo-inositol, DL-Pipecolic acid, and cytosine between AMI and control groups. Regarding biostatistical analysis results, creatinine, glutamine, myo-inositol, and DL-Pipecolic acid levels were significantly higher in the AMI group compared to the control group.

The GBT model was created as part of artificial intelligence/machine learning modeling to forecast the existence or lack of AMI based on the differentially expressed metabolites. With an area under the curve (AUC) of 0.92, the five metabolites and the proposed diagnostic model (GBT) successfully distinguished between AMI and healthy individuals in both the discovery and validation datasets. The five lipid metabolites may be used as potential biomarkers to distinguish between people with AMI and healthy people, according to the GBT model findings. In a previous study on the prognosis of AMI, 25 lipid metabolites were found among the 795 lipid compounds that were expressed in various ways, with particular expression in the AMI group compared to the healthy control (HC) and unstable angina (UA) groups [22]. Unlike the above study, we employed the LIME technique to interpret the predictions of the proposed model for discriminating AMI and control individuals. Thus, individualized assessments can be made by obtaining specific predictions of AMI and control subjects using the values or ranges of the selected five metabolites.

Wang X et al. investigated differential metabolites with a tissue metabolomics approach based on gas chromatography-mass spectrometry (GC-MS) and examined their diagnostic potential for MI. The related research findings confirmed that especially glutamine, glutamate, and lactate together provide a suitable potential for MI diagnosis [23]. In the current study, creatinine, glutamine, myo-inositol, DL-Pipecolic acid, and cytosine were differentially expressed metabolites on the results of analytical analysis, and cut-off points were calculated for the identified metabolites based on the XAI outputs. In our results, the importance coefficient of glutamine for diagnosing AMI was 0.052, which was at the lowest level compared to other metabolites.

According to research by Duerr et al., postconditioning with the TLR9 ligand 1668-thioate (CpG) may affect inflammation and remodeling in reperfused murine MI. The treatment resulted in less remodeling in CpG, which showed a cardioprotective impact. The LV function was preserved and the poor LV remodeling was attenuated in this instance [24]. Regarding cytosine levels in the AMI group compared to the control group, there was no statistically significant variation between the groups in the current study. However, cytosine<=861.67 was the cut-off point for the AMI group and 861.67<cytosine<=164169.71 for the healthy control group. The proposed GBT model differentiated the patients under investigation with 100% accuracy. When FC values were examined, cytosine level was 1.53-fold up-regulated in the AMI group compared to the control group. In our results, cytosine was an essential metabolite in determining the prognosis of AMI.

2250 patients with AMI were followed for an average of 1 year in one of the two trials on creatinine. A higher baseline serum albumin-to-creatinine ratio (sACR) was associated with a decreased chance of in-hospital all-cause mortality, cardiac death, and other adverse outcomes. Patients with low sACR had higher rates of cardiac death, all-cause mortality, and other negative effects during the follow-up time than those with high sACR [25]. In another study, the blood urea nitrogen/creatinine ratio (BUN/Cr) did better at predicting the prognosis of people with acute heart failure than either BUN or creatinine alone (AHF). An increased risk of mortality in individuals with AMI has been linked to AHF with high BUN/Cr [26]. As reported in these two studies, the ratio of creatinine to albumin and nitrogen

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was influential in determining the prognosis of AMI. In this study, FC value for creatinine was 0.50-fold down-regulated in the AMI group, and creatinine alone was the least important of the five metabolites in determining the prognosis of AMI.

McKirnan et al. found that blood myo-inositol levels rose and cardiac tissue signals reduced to varied degrees in MI rabbits in their rabbit MI model research. Decreased tissue myo-inositol in the rabbit MI model implies probable alterations in lipid metabolism [27]. As reported in this study, myo-inositol levels affect lipid metabolism, which is important for the cell membrane. As a result, it may affect LV remodeling after AMI. In our study, myo-inositol levels were significantly higher in AMI patients than in the control group. This result may also be important for LV remodeling after AMI.

Beuther et al. identified a cluster metabolite comprising four amino acids (arginine, glutamine, pipecolic acid, and taurine) as promising to mediate the atheroprotective action against the development of atherosclerosis in a study of 2160 persons [28]. In this study, DL-pipecolic acid has distinctive importance for diagnosing AMI.

In the retrospective follow-up of male and female patients with heart diseases, Usalp S. found that left ventricular ejection fraction decreased in both genders and that gender was an independent risk factor for coronary artery disease [29]. In our study, AMI patients could not be evaluated as gender specific.

Limitations

The most important limitation of our study is that the demographic data of the patients could not be accessed.

Conclusion

Findings of metabolomics data and XAI analyses revealed that five lipid metabolites may be used as potential predictors of AMI. The proposed GBT model can predict AMI based on the selected metabolites as a computer-aided diagnosis system. Further clinical studies may be recommended on the possible effects of cytosine, glutamine, and myo-inositol metabolites on LV remodeling to determine prognosis after AMI.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

This study does not require ethics statement. Since I used the previously published data of the following studies. The relevant data are accessible on the National Metabolomics Data Repository (NMDR) website, the Metabolomics Workbench, https://www.metabolomicsworkbench.org, where it has been assigned Project ID (PR001202). The data is available directly through its Project DOI: (10.21228/M8BD7S). At the NIH Common Fund's National Metabolomics Data Repository (NMDR) website, the Metabolomics Workbench, https://www.metabolomicsworkbench.org, where it has been assigned Project ID (PR001202). The data is available directly through Project DOI: (10.21228/M8BD7S).

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