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FENDRR: A Long Non-coding RNA as a novel Biomarker for Acute Myocardial Infarction

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Abstract

Acute myocardial infarction is a main cause of death all over the worldwide which is recognized by decreased of blood supply to the myocardium due to a lack of oxygen and blockage in the arteries. Many studies aimed to early diagnosis of acute myocardial infarction to avoid its danger. We aimed to evaluate the predictive influence of long non-coding RNAs expression in Acute myocardial infarction. Using in silico data analysis to retrieve LncRNAs related to Acute myocardial infarction that result in selection of LncRNA_FENDRR (Foxf1 adjacent non-coding development regulatory RNA) expression of the serum non-coding RNAs in 25 healthy volunteers, 20 patients with chest pain due to non- cardiac causes and 65 patients with acute myocardial infarction by using quantitative real-time PCR. The study data analysis shows significant down regulation in the expression of serum levels of LncRNA_FENDRR in patients with Acute myocardial infarction compared with healthy volunteers. Our study state thatLncRNA_FENDRR appears to be a novel non-invasive biomarker that could early detect AMI that could improve health outcome.

Keywords: Acute myocardial infarction, long non-coding RNA, FENDRR, Real-time PCR.

1. Introduction

Cardiovascular diseases especially acute myocardial infarction (AMI) is the first leading cause of death all over the world. AMI affects more than three million people worldwide**(Nascimento *et al.*, 2019)**. Acute myocardial infarction is the medical term for a heart attack that is severe. MI occurs when blood flow to a portion of the heart becomes obstructed, causing injury to the heart muscle due to absence of oxygen. Due to an unstable build-up of plaques, white blood cells, cholesterol, and fats, one of the coronary arteries that delivers blood to the heart becomes blocked**(Lu *et al.*, 2015)**.

Currently, biomarkers from circulatory systems, primarily the blood circulatory system, such as troponins, CK-MB, and myoglobin, are commonly employed in the clinical diagnosis of AMI **(Saunders *et al.*, 2011)**. Researchers are now focusing their efforts on the RNA especially the non-coding. With the widespread of use of microarray and next-generation RNA sequencing technologies, there is growing evidence that noncoding RNAs have a role in illness progression. Noncoding RNAs in the blood could be used as a marker for disease progression, prognosis and as potential therapeutic targets for numerous diseases, including cardiovascular diseases. These RNAs are more stable in the peripheral circulation and organ-specific than protein markers **(Shi *et al.*, 2016 – Lu and Thum, 2019).**

So, in this study we hope to select from the long non-coding RNAs that can be used as a novel genetic non-invasive biomarker for AMI for early detection of AMI and avoid the conflict by traditional cardiac biomarkers.

2. Review of Literature

Acute myocardial infarction results in irreversible damage to the heart muscle due to an absence of oxygen. Furthermore, a MI can result in a variety of serious complications. The key is to restore blood flow and reperfusion of the heart. The better the prognosis, the earlier the treatment**(Mechanic *et al.*, 2022)**. Egypt, which is classified as an LMIC by the World Bank, has a

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CVD mortality rate of 40 % per year**(Reda *et al.*, 2021)**.

As known that the human genome consists of 98.5% of junk DNA that don't code proteins**(Comings, 1972)**. Part of non-protein coding DNA is transcribed into what called non-coding RNAs which is a group of heterogeneous functional RNA**(Carninci and Hayashizak, 2007)**. LncRNAs, which range in length from 200 to more than10000 nucleotides, lack the ability to code for proteins because they lack open reading frames. LncRNAs have been shown to play a role in a variety of physiological and pathological processes in cardiovascular diseases (CVDs), including heart failure, cardiac hypertrophy, and cardiometabolic disorders, and are mostly connected to epigenetic, transcriptional, and posttranscriptional control**(Song *et al.*, 2020**).

FENDRR that is well-known Foxf1 adjacent non-coding development regulatory RNA. FENDRR is a lncRNA that has been linked to heart development has the function of guide lncRNA. The lncRNA FOXF1 forms a compound with PRC2, which binds to specific locations in the promoters of FOXF1 and PITX2 that suppresses their expression. It also binds to trithorax group/mixed lineage leukemia complexes (TrxG/MLL) to regulate chromatin shape and gene activity. Although FENDRR is required for healthy heart and body wall development in mice, there is no conclusive evidence that it plays a function in CVD**(Grote *et al.*, 2013)**.

3. Materials and Methods

3.1. Specimens

The specimens collected in this study were human blood samples with total number of 110 samples, where the collection procedures were approved by the Research Ethical Committee of Faculty of Medicine, Ain Shams University, Egypt. The specimens were collected from January 2019 up to January 2020. All samples were classified into three groups: 25 of Healthy controls, 20 non-cardiac patients who were suffering from chest pain but after examination and some analytical tests, they were diagnosed as non-cardiac chest pain and 65 of acute myocardial infraction documented patients recruited from Ain Shams University Hospital with acute and ongoing chest pain for 8 hours. AMI was diagnosed on the basis of elevated serum Troponin levels, CKMB in addition to Clinical symptoms & history consistent.we have excluded patients with history of hepatitis, end-stage renal failure,congenital heart disease, bleeding disorders, previousthorax irradiation therapy, or malignant disease from ourstudy.

3.2.Biochemical parameters investigation

Estimation of creatinine, total cholesterol, HDL, LDL, and triglycerides using specific kits from Bio-diagnostic Co., Egypt. Also, determination of cardiac parameters: CK-MB [DiaSys Diagnostic Systems, Germany], troponin [Abcam, UK.]

3.3. In silico data analysis

FENDRR lncRNA was chosen based on in silico data, it was known its function in inflammation, fibrosis, and cardiovascular disorders **(Karolina *et al.*, 2012 – Nicholse*t al.*,2014)**.

3.4. Detection of serum long non-coding RNA (FENDRR)

3.4.1 Purification of total RNA

QIAamp® RNA Blood For total RNA purification from human whole blood kit [QIAGEN, CA, USA] was used according to the manual.Nanodrop™ 2000 Spectrophotometer [Thermo Scientific™, USA] and Qubit® 3.0 Fluorometer [Invitrogen, Thermo Fisher Scientific, USA]were used for concentration and purity assessment of RNA samples.

3.4.2 Quantitative real time-PCR

RT-PCR was carried out using TaqMan® Small RNA Assays [AB Applied Biosystem, USA.] to construct cDNA then using RT2 SYBR Green ROX qPCR Master mix[Qiagen, Germany] and Hs-ACTB-1-RT2 QuantiTect Primer Assays [Qiagen, Germany] as internal controlusing Applied biosystem 7500 fast real time PCR system [AppliedBiosystem, USA]. We used the relative quantification of geneexpression methods to calculate RQ = $2^{-\Delta\Delta C_t}$using Livak method**(Livak and Schmittgen, 2001)** with consideration the negative expression if C_t value was ≥ 36.

3.4. statistical analysis

Analysis of data was performed with IBM SPSS Statistics Version 25for Windows (SPSS Inc., IBM Corporation, NY, USA). In order to verify normal distribution of data the Shapiro-Wilk test was used to test normality hypothesis of all quantitative variables for furtherchoice of appropriate parametric and non-parametric tests. Quantitative variables which had normal distribution were described by the Mean, Standard deviation (SD). While, quantitative variables which had nonnormal distribution were described by the median. Parametric and non-parametric tests was applied. The ROC curve was used to evaluate the predictive values for different biomarkers. Also, chi-square test and Pearson correlation test were used. All statistical tests were 2-tailed and a *P*-value $\leq$ 0.05 was considered statistically significant **(Shapiro and wilks, 1965 - Razali and Whai, 2011)**.

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4. Results

4.1. Demographic parameters

There was no significant difference in the studied groups as regards age and sex distribution while a significant difference for BMI **(Tables 1&2**).

Table (1): Distribution of gender among the healthy control, non-cardiac, and acute myocardial infarction groups:

Groups	N	Gender		*Chi-square*	*P*-value
		Males	Females		
		Count (%)	Count (%)		
Healthy Control	25	20 (80%)	5 (20%)	0.247	0.884
Non-cardiac	20	15 (75%)	5 (25%)		
Acute myocardial infarction	65	52 (80%)	13 (20%)		

Table (2): Mean values of age and BMI of the healthy control, non-cardiac, and acute myocardial infarction groups:

Parameters	Groups	N	Mean ± S.D.	Range	*F*	*P* - value
Age (years)	Healthy Control	25	54.60 ± 9.66[a]	46	0.200	0.819
	Non-cardiac	20	56.5 ± 10.98[a]	55		
	AMI	65	55.94 ± 11.15[a]	55		
BMI (kg/m2)	Healthy Control	25	25.04 ± 1.79[a]	5	5.518	0.005*
	Non-cardiac chest pain	20	26.75 ± 2.69[b]	8		
	AMI	65	27.24 ± 3.15[b]	16.8		

• AMI (Acute myocardial infarction)
• All data are presented as mean ± standard deviation (Mean ± SD).
• All data were subjected to one way ANOVA followed by post hoc test (Duncan) at $P \leq 0.05$.
• * *P*- value is significant.

4.2. Clinical and biochemical data of the study

In this study, we have not found any differences amongthe three investigated groups *i.e.*,LDL, HDL, and ($P>0.05$), but in serum creatinine, total cholesterol, total Triglycerides, CK-MBand cardiac troponin showed marked differences andthe details are shown in **(Tables3, 4 &5)**.

Table (3): Median values of serum creatinine of the healthy control, non-cardiac, and acute myocardial infarction groups:

Parameters	Groups	N	Median	*P*-value
Creatinine (mg/dL)	Healthy Control	25	1.1[a]	0.009**
	Non-cardiac	20	1.1[ab]	
	Acute myocardial infarction	65	1.3[c]	

• All data are presented as median.
• Kruskal-Wallis Range Test, Level of significance is $P< 0.05$
• ** *P*- value is highly significant.

Table (4): Mean values ± S.D. of lipid profile of the healthy control, non-cardiac, and acute myocardial infarction groups:

Parameters	Groups	N	Mean ± S.D.	Range	*F*	*P*-value
Total cholesterol (mg/dL)	Healthy Control	25	195.6 ± 29.73[a]	90	3.635	0.030*
	Non-cardiac	20	200.25 ± 30.24[ab]	90		
	AMI	65	213.75 ± 32.17[b]	135		
HDL (mg/dL)	Healthy Control	25	35.36 ± 9.87[a]	28	2.310	0.104
	Non-cardiac	20	33.30 ± 7.76[a]	28		
	AMI	65	31.68 ± 6.03[a]	23		
LDL (mg/dL)	Healthy Control	25	116.28 ± 20.89[a]	79	1.582	0.210
	Non-cardiac	20	119.85 ± 26.23[a]	105		
	AMI	65	127.26 ± 30.77[a]	134		
Triglycerides (mg/dL)	Healthy Control	25	72.04 ± 28.45[a]	83	32.360	0.000**
	Non-cardiac	20	67.55 ± 28.90[a]	100		
	AMI	65	131.52 ± 45.28[b]	197		

• All data are presented as mean ± standard deviation (Mean ± SD).
• All data were subjected to one way ANOVA followed by post hoc test (Duncan) at $P \leq 0.05$. Statistical analysis.
• * *P*- value is significant.
• ** *P*- value is highly significant.

Table (5): Median values of serum CK-MB,serum troponin of the healthy control, non-cardiac chest pain, and acute myocardial infarction groups:

Parameters	Groups	N	Median	*P*-value
CK-MB (U/L)	Healthy Control	25	8[a]	0.000**
	Non-cardiac chest pain	20	28.5[b]	
	AMI	65	33[b]	
Troponin (Pg/mL)	Healthy Control	25	0.2[a]	0.000**
	Non-cardiac	20	0.75[a]	
	AMI	65	39[b]	

• All data are presented as median.
• Kruskal-Wallis Range Test, Level of significance is $P< 0.05$.
• ** *P*- value is highly significant.

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4.3. Relative expression of serumLncRNA_FENDRR among the Study Groups

Compared to the healthy control group, the expression levels of LncRNA_FENDRR was highly significantly decreased in the noncardiac chest pain, and acute myocardial infarction groups by –66.55% and -99.15% respectively. Moreover, the expression of LncRNA_FENDRR give a high statistical significance according to Kruskal-Wallis Range Test between the AMI group against other groups as shown in **Table 6 and figure 1** in details.

Table (6): Median values of the serum for LncRNA_FENDRR, of the healthy control, non-cardiac, and acute myocardial infarction groups:

Parameters	Groups	N	Median	*P*-value
LncRNA_FENDRR	Healthy Control	25	16.5[a]	0.000**
	Non-cardiac	20	5.52[a]	
	AMI	65	0.14[b]	

• All data are presented as median.
• Kruskal-Wallis Range Test, Level of significance is *P*< 0.05.
• ** *P*- value is highly significant.

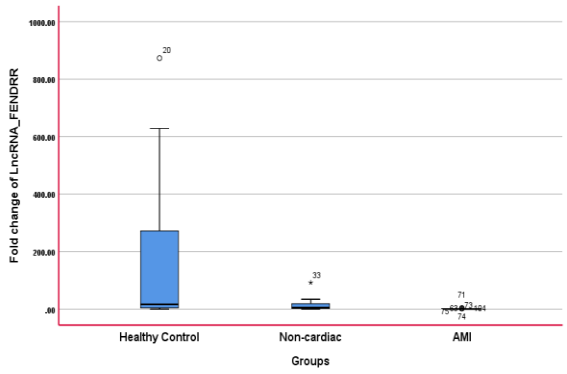

Figure (1): Boxplot for fold change expression of serum LncRNA_FENDRR in the Healthy control, non-cardiac, and AMI groups.

4.4. Correlation between serum LncRNA FENDRR and other studied parameters:

Using Spearman correlation test, **Table 7** shows the correlation between the long non-coding RNA FENDRR with all other studied parameters in different subjected groups. No statisticallysignificant difference between LncRNA_FENDRR and all parameters among studied groups except there were only between LncRNA_FENDRR and cardiac markers (CK-MB and troponin) in the AMI group.Negative significant correlations were found between theexpression of LncRNA_FENDRR and levels of CK-MB and troponin levels in the AMI group as *P*= 0.017 and *P* = 0 respectively **(Figures 2 and 3)**.

Table (7): Correlation between LncRNA FENDRR and other studied parameters in the healthy control, non-cardiac, and acute myocardial infarction groups.:

	LncRNA_FENDRR		
	Healthy control	**Non-cardiac chest pain**	**Acute myocardial infarction**
	r (*P*-value)	**r (*P*-value)**	**r (*P*-value)**
Sex	-0.208 (0.319)	-0.277 (0.237)	0.036 (0.777)
Age	0.236 (0.255)	-0.058 (0.807)	0.150 (0.232)
BMI	0.149 (0.478)	-0.070 (0.768)	-0.047 (0.709)
Cholesterol	0.255 (0.219)	-0.016 (0.948)	-0.210 (0.093)
Triglycerides	0.128 (0.541)	-0.026 (0.913)	0.086 (0.498)
HDL	-0.209 (0.316)	-0.204 (0.389)	0.188 (0.134)
LDL	0.369 (0.069)	0.200 (0.398)	-0.069 (0.584)
Creatinine	-0.009 (0.968)	-0.049 (0.836)	-0.078 (0.538)
CKMB	0.078 (0.711)	0.296 (0.205)	**-0.295- (0.017) ***
Troponin	-0.118 (0.575)	-0.114 (0.633)	**-0.517- (0.000) ****

•Statistical analysis was performed by Spearman correlation, *P*-value≤0.05
• ** *P*-value≤0.001, highly significance.

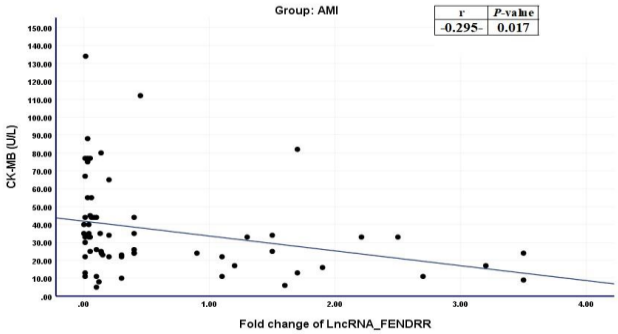

Figure (2): Correlation between expression of serum LncRNA_FENDRR and serum CK-MB concentrations in the acute myocardial infarction group.

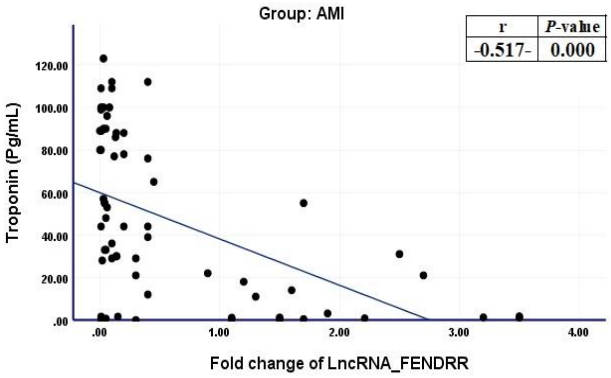

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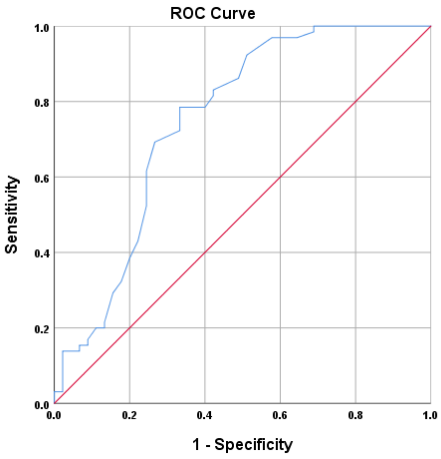
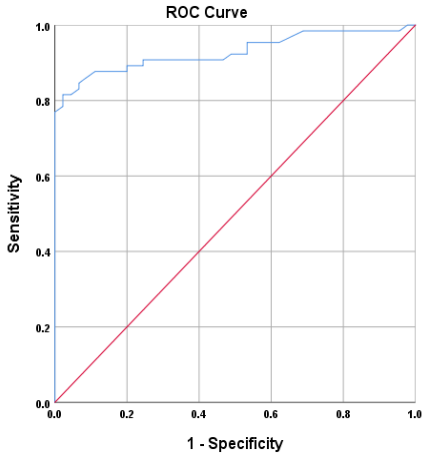
Figure (3): Correlation between expression of serum LncRNA_FENDRR and serum troponin levels among the AMI group.

4.5. ROC curve for different studied serum cardiac parameters to give the evidence as a potential diagnostic biomarker for AMI:

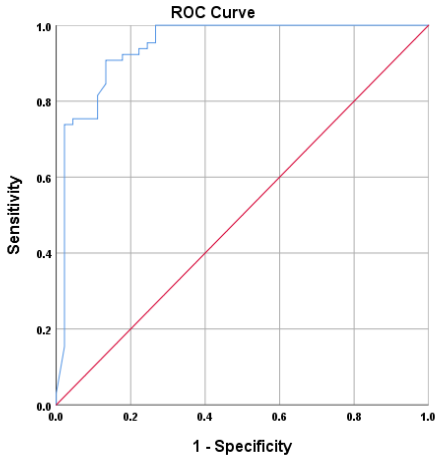
In construction of the ROC curves, we considered the healthy control and the non-cardiac groups as the control group to be compared with the AMI group.**Figure 4 and Table 8** illustrate the ROC curves of the CKMB level, troponin concentration, and circulating expression levels of LncRNA_FENDRR to discriminate AMI patients from healthy controls. CK-MB levels gives the lowest diagnostic efficacy among the different parameters with AUC of 0.749 (95% CI:.0.649-0.849, P=0.000) that can give as high as 73.7 % sensitivity and 69.2 % specificity at a cut off of 23.5 **(figure 4A).**However, **Figure 4B** shows that the AUC of troponin was 0.929 (95% CI:.0.879-0.978, P=0.000) with a cut-off point of 1.45 which could yield a sensitivity of 97.8% and specificity of 81.5%. On the other hand, LncRNA_FENDRR with an area under curve (AUC) of 0.944 (95% CI:0.897-0.991, P=0.000) and an optimal cutoff point of 1.94 that associated with 86.7% sensitivity and 90.8% specificity as shown in **figure 4C**.



(4A)



(4B)



(4C)

Figure (4): ROC curves of the serum (A) CK-MB, (B) Troponin and (C) LncRNA_FENDRR expression to discriminate AMI patients from control.

Table (8): Performance characteristics of cardiac biomarkers collected from ROC curve analysis:

Parameters	Sensitivity (%)	Specificity (%)	PPV (Positive Predictive Value) (%)	NPV (Negative Predictive Value) (%)	Accuracy (%)
CK-MB	73.7 %	69.2 %	78.9 %	62.3 %	70.9 %
Troponin	97.8 %	81.5 %	98.1 %	78.6 %	88.2 %
LncRNA_FENDRR	86.7 %	90.8 %	86.7 %	90.7 %	89.1 %

4.6. Positivity rate of serum investigated parameters based among the study groups:

From the ROC curves and the chosen cut-off points for each parameter, chi-square test has been carried out for our data are shown in **Table (9)**:
for healthy control people, they should give negative result with CK-MB and troponin while they give positive with expression of LncRNA_FENDRR.
• All parameters give high statistical significance (P<0.001). In the expression of LncRNA_FENDRR, the data obtained gives 88%, 85%, 90.77% of true

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positivity for healthy control, non-cardiac chest pain and the AMI groups respectively.

Table (9): Positivity rate of serum investigated cardiac parameters based on the data and cut-off point from ROC curves analysis among the study groups:

Groups		Cardiac parameters		
		CK-MB	Troponin	LncRNA_FENDRR
		N (%)	N (%)	N (%)
Healthy Control (N=25)	Positive	1 (4%)	0 (0%)	22 (88%)
	Negative	24 (96%)	25 (100%)	3 (12%)
Non- cardiac (N=20)	Positive	11 (55%)	1 (5%)	17 (85%)
	Negative	9 (45%)	19 (95%)	3 (15%)
Acute myocardial infarction (N=65)	Positive	45 (69.23%)	53 (81.54%)	6 (9.23%)
	Negative	20 (30.77%)	12 (18.46%)	59 (90.77%)
	X2	30.871	67.047	66.001
	P - value	0.000**	0.000**	0.000**

• ** *P*-value≤0.001, highly significance.

5. Discussion

Acute myocardial infarction (AMI) is one of the most common coronary artery diseases (CAD) complications that results in death**(Mathers and Loncar, 2006)**. Pathologically, acute coronary syndrome develops so-called plaques, ulceration, and hemorrhage, followed by complete or in-complete occlusive thrombosis. Many well-known factors include smoking, drinking alcohol, diabetes, dyslipidemia and advanced age**(Roeters van Lennepet al., 2002).**

Early and rapid detection, diagnosis, and early prevention of acute myocardial infarction are demanded to stop the progressive development of AMI especially its treatment and prognostic evaluation mainly depend upon the severity of the coronary lesions assessed by coronary angiography, an invasive and expensive test. Thus, leads to effective therapy and prevention of adverse progression of AMI to improves survival of patients**(Lozano et al., 2012)**.

As ECG is an important tool for diagnosis of AMI, it has limited sensitivity (50-60%) detection**(*Li et al.*,2017)**. Also, unfortunately many false elevations of protein cardiac markers in skeletal muscle injury, cardiac trauma and end-stage of renal disease**(Haghighi*et al.*, 2014)**, Therefore, searching for novel biomarkers that are directly linked to AMI detection with high accuracy as well as high sensitivity at a biochemical and molecular levels has the most consideration point in current researches.

Only about 2% protein-encoding genes, on the other hand the enormous majority of the human genome is made up of non-coding RNAs (ncRNAs)**(Ponting and Belgard ,2010)**. It was suggested that theses ncRNA are of great values in gene-expression patterns, diverse biological processes like enzyme-activity control, inhibition of transcription regulators, and regulation of mRNA transcription**(Guttman and Rinn, 2012).**Long non-coding RNA was suggested for regulation cardiac development and has a role in cardiac insufficiency**(Storino Farina et al., 2015)**. So, ncRNAs can be used a new biomarker for diagnosis of AMI**(Navickaset al.,2016).**

In this study, sex and age were found with no significance (*P*>0.05) between different studied group. While Body mass index (BMI) has a statistical significance between groups (*P*= 0.01), so we must control the obesity to decrease occurrence of AMI and this agree with**Zhuet al., 2014**.

There are many pieces of evidence that AMI patients suffer from dyslipidemia. In our study, the results of lipid profile analysis show increase in concentration of serum total cholesterol and LDL, decrease in concentration of HDL, and high increase level of serum triglycerides in the group of AMI patients compared to the healthy and non- cardiac groups. Only total cholesterol (*P* = 0.03) and triglycerides (*P* = 0.000) show a high statistical significance. These results are convenient for **Kumar et al., 2009** and **Balci, 2011.**

As troponin-T and CK-MB are the most widely enzymatic cardiac test used for diagnosis and following up the AMI, they were measured in our study. Troponins are a three-protein component complex found in skeletal and cardiac muscle. Especially troponin T that is one of the three subunits, its levels differ in the skeletal muscle and cardiac muscle on opposite to Troponin C which are the same in both muscles so can be highly specific for cardiac muscle necrosis**(Thygesen *et al.*, 2018).** CK is an enzyme that is present chiefly in the cardiac muscle and skeletal muscle. CK-MB, one of its three isoenzymes of CK is the cardiac muscle portion **(Bloomberg *et al.*, 1975)**. The advantage of CK-MB over the troponins is the early clearance that aids in the finding of reinfarction**(Gerhardt *et al.*, 1991)**.For cardiac markers: CK-MB and troponin, our study shows a highly statistical significance (*P*<0.001) in-between the subjected groups as their level are increased in AMI group compared with healthy one. These results contrary with **Voss et al.,1995** and agreed with **Tucker *et al.*,1997** and**Gerhardt *et al.*, 1991**. However, in a healthy population, the increased sensitivity of hs-cTnT increases the likelihood of false positives**(Schulte *et al.*, 2020)**, so there is a need to improve and enhancement current biomarkers, with using molecular biomarker as circulating non-coding RNA that are potentially contributing to the specificity of protein biomarkers.

Non-coding RNAs are subdivided into two major classes: long RNA and short RNA**(Kapranov *et al.*,2007)**. As many studies have shading on the role of non-coding RNA (long or micro) especially

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the circulating ones as biomarker in most cases of coronary vascular diseases in particular AMI that consider our study **(Das et al., 2020)**. Using in-silico data analysis to choose a noncoding long RNA. We aim to evaluate the diagnostic accuracy in early detection of AMI patients that give false results with cardiac enzymes tests for LncRNA_FENDRR for myocardial development marker.

The LncRNA_FENDRR gene which is consists of 3099 nucleotidesin length, located at chr3q13.31**(Zheng et al.,2021)**.There is no much information about it but some studies considered that it hasa role in heart and body wall development**(Grote et al., 2013)** also it showeddecreased in expression in patients with atherosclerosis**(Çekin et al., 2018)**.From our results, there were downregulation of the studied long non-codingRNA (LncRNA_FENDRR) expression in the AMI patients when comparingwith the healthy control and non-cardiac groups and this agree with **Çekin.**

After data analysis using the different statistical tests, we can consider the studied non-coding RNA (LncRNA_FENDRR) as a new biomarker that can be used in the early detection and diagnosis of AMI patients especially with cases that make conflict with CKMB and troponin tests.

6. Conclusions

In our study, we reported downregulation of lncRNA-FENDRR expression in AMI group compared with other groups. In conclusion,LncRNA_FENDRR expression can be a novel non-invasive biomarker for diagnosis of AMI. Searching for other novel non-coding RNAs to use as novel biomarkers for early diagnosis of AMI can be carried out.

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