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Cardiac Markers: An Index in the Assessment of Cardiovascular Disease in Diabetic Patients in Bayelsa State, Niger Delta Region, South of Nigeria

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Abstract

Background and Objective: Patients with type 2 Diabetes mellitus (DM) are known to be at risk of developing cardiovascular diseases (CVD). The prevalence and incidence of DM patients with heart diseases is unknown in Yenagoa and its environ of Bayelsa State, Niger Delta Region of Nigeria. The study, with the tool of cardiac markers, investigated the incidence of CVD in chronic and non-chronic DM patients and compared the prevalence in both male and female subjects with respect to the duration of illness. The study sought to evaluate the diagnostic performance of cardiac markers to evaluate the diabetic subjects and the goals of screening are to improve life expectancy and quality of life by preventing Myocardial infarction (MI) and heart failure through the early detection of significant CVD. **Study Design and Methods:** A total of 356 type 2 DM patients were recruited for the study. They are diabetic patients that presented with symptoms of CVD. They were grouped into 135 DM patients that have suffered the Diabetes for less than 10 years, 119 for 10 - 20 years and 102 for 21 and above years. The plasma levels of the Cardiac Markers, Troponin I (CTnI), Troponin T (cTnT), Creatine Kinase (CK-MB), Myoglobin (MYO) and Lactate dehydrogenase (LDH) were determined in the subjects. The method of fluorescence immunoassay (FIA) was used in the measurement of CTn1, CTnT and MYO. Enzyme Linked Immunosorbent Assay (ELISA) was used to determine the CK-MB and LDH. **Results:** Analysis of the results has shown that 14.33% of the studied subjects were diagnosed of various CVD and were statistically significant ($p < 0.05$). Of these, 8.15% were females and 6.18% were males. 54.90% of DM subjects diagnosed of CVD were from group 21 and above years while 29.41% were from group

10 to 20 years and 15.69% from those that had suffered it for <10 years. 26.12% of the total DM patients studied had either one or more of the cardiac markers elevated, showing the potentials of developing heart diseases. The correlation between the different age groups and the pair wise correlations between measured parameters in the DM patients with CVD showed a positive correlation. **Conclusion:** The tools of cardiac markers can be used in the diagnosis/assessment of CVD in type 2 DM patients. The risk of developing CVD is more in females than the male subjects that are suffering from type 2 DM and those with long duration of the illness in Yenegoa, Bayelsa State, Niger Delta Region, South of Nigeria.

Keywords

Diabetes Mellitus, Cardiovascular, Troponins, Creatine Kinase, Myoglobin, Lactate Dehydrogenase, Immunoassay

1. Introduction

Diabetes mellitus (DM) is a metabolic disease which is characterised by absolute or relative deficiency in insulin secretion, insulin action or both [1]. This leads to glucose underutilization with concomitant diabetic complication and oxidative stress [2]. The Oxidative stress is as a result of increase in production of free radicals or decreased level of antioxidants [3]. Oxidative stress plays a pivotal role in the development of diabetes complications, both microvascular and cardiovascular. The metabolic abnormalities of diabetes cause mitochondrial superoxide over production in endothelial cells of both large and small vessels as well as in the myocardium. The increased superoxide production causes the activation of 5 major pathways involved in the pathogenesis of complications [4] [5] [6].

Diabetes mellitus in chronic conditions is a risk factor in developing coronary heart disease (CHD) and other cardiovascular diseases (CVD) [7]. They are at increased risk for developing heart disease and are often present at an earlier age than people without diabetes [8]. Furthermore people with diabetes have a high prevalence of silent myocardial Ischemia [9] and almost one third of myocardial infarctions occur without recognised or typical symptoms. Whether the patients suffer from type 1 or type 2 diabetes, along with the patients' age and duration of time living with diabetes, will impact the risk for developing cardiovascular disease, as diabetes itself is a powerful risk factor for the future development of CVD [10] [11]. In patients with type 2 diabetes, CVD becomes the leading cause of death after 10 years of duration and accounts for 40 percent of all deaths after 20 years of duration [12].

Most studies on cardiovascular risk in patients with diabetes have been performed in patients with type 2 diabetes, who are typically older at disease onset than those with type 1 diabetes [8] [12]. In Nigeria, the factors like the socio-economic

status (SES) an important component of the socio-economic gradient in CVD are present [13].

According to World Health Organisation (WHO), about 11% of deaths in Nigeria are related to cardiovascular disease and 1% of these are associated with diabetes [14]. The death rate from infectious disease has been decreasing slowly in Nigeria largely due to its prevention, but death due to chronic disease has been increasing rapidly. Cardiovascular disease has been major problem in the developed and developing countries.

In Nigeria, particularly the Bayelsa State, South of Nigeria with majority of the population being civil servants and artisan farmers, the burden of the CVD is overwhelming and data on the prevalence/incidence of CVD on diabetes mellitus patients are lacking with obvious increase in the mortality rate. Most of the studies [15] [16] [17] conducted in the developing countries are not applicable in the environment of this study due to problems of under or over estimations [16]. This study focused on the incidence of CVD in chronic DM patients using the tools of cardiac markers.

Cardiac markers are used in the diagnosis and risk stratification of patients suspected with different kinds of CVD symptoms that include chest pain and acute coronary syndrome [18]. The cardiac troponins are regulatory proteins found in skeletal and cardiac muscle with identified three subunits; Troponin 1 (Tn1), Troponin T (TnT) and Troponin C (TnC) [19]. The skeletal and cardiac subforms for Tn1 and TnT are distinct, hence their use for this study because immunoassays have been designed to differentiate between the two [20] [21]. Before the advent of cardiac troponins, the biomarker of choice for the diagnosis of acute MI was the Creatine Kinase, CK-MB isoenzyme. It exists as 2 isoforms; CK-MB1 and CK-MB2. The Laboratory determination of this biomarker (CK-MB) actually represents the simple sum of the 1 and 2 [22]. Myoglobin (Myo) is a heme protein found in skeletal and cardiac muscle that has been used also in the diagnosis of early MI. Though not very cardio specific, its laboratory assay has aided in the diagnosis of MI [23]. Lactate dehydrogenase (LDH) is an enzyme involved in energy production that it is found in almost all of the body cells, with the highest levels found in the cells of the heart. The LDH has isoforms and is non cardio specific, but is Laboratory determination has been found to be useful in the diagnosis of heart diseases [24].

These biomarkers have the Characteristic (accuracy, precision, high sensitivity and specificity) that will be objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or even pharmacologic response to a therapeutic intervention in type 2 Diabetic subjects been studied. The studies [13] [25] [26] on the associated risk factors will help in reducing the risk of developing CVD in diabetes.

2. Materials/Methods

Study area:

The study was conducted on patients suffering from diabetes mellitus disease population attending the Federal Medical Centre Yanagoa, Bayelsa State capital and Niger Delta University Teaching Hospital (NDUTH) Okolobiri and other diabetic clinics in Bayelsa State, Niger Delta Region of Nigeria between the months of June 2014 to May 2018.

2.1. Study Population

A total of 356 chronic and non-chronic Diabetes patients were recruited for this study. This comprised of 197 females (55.34%) and 159 males (44.66%) diabetic patients. A total of 135 of the subjects have suffered the disease for less than ten years, 119 of them for 10 - 20 years and 102 for 21 and above years. Inclusion criteria were identified type 2 DM patients that presented with symptoms of different heart diseases. Those without symptoms of heart diseases were excluded from the study.

2.2. Ethical Consideration

Ethical approval was gotten from the University's institution committee for Human Research and approval from the patients before sample collection. Before sample collection, a talk was given to the patients on the essence and significance of the study. A demographic/questionnaire was issued to them concerning age, sex, duration of illness, medical symptoms and nature of drugs for management among others.

2.3. Sample Collection

About 10.0 ml of venous blood was drawn from the patients using standard vene-puncture technique after overnight fast and discharged into a tube. The sample was separated for fasting blood sugar (FBS) and cardiac markers determination. This was allowed to clot for about half an hour and then centrifuged at 1500 rpm for about 10 minutes. The serum was separated into a plain tube and analysis of the different cardiac markers performed within 14 hours of sample collection.

2.4. Blood Test

Fasting Blood Sugar (FBS):

The fasting blood glucose levels were performed on all the patients' samples using the glucose oxidase method as modified by Randox Laboratories Limited (United Kingdom) [27].

2.5. Assay for Troponins and Myoglobin

The serum Troponin I CTn1) and T (CTnT), and myoglobin (Myo) were determined using the Fluorescence immune technique. It uses a sandwich immunodetection method. The more antigens in samples forms, the more antigen-antibody complex and leads to strong intensity of fluorescence on detector antibody that is measured [28] [29].

2.6. Assay for Creatine Kinase (CK-MB) and Lactate Dehydrogenase (LDH)

The Enzyme Linked Immunosorbent Assay (ELISA) method [30] was used in the quantitation of the serum CK-MB and LDH. Specifically, the Elabscience assay kit (USA) and the Biotechnologies plate reader were the analytical instruments used. It is a high sensitive and specific biochemical test kits applied for the detection of myocardial enzymes.

2.7. Statistical Analysis

The data are expressed as mean ± standard deviation, standard error of mean and normal ranges. Correlation between the groups studied was tested using the regression analysis. The results obtained from this were subjected to statistical analysis using standard computerized analysis tool of ANOVA: two factors without replication and standard t-test: pair two samples for mean. 95% confidence level ($p < 0.05$) were used and considered significant.

3. Results

The result of the study, using the tools of the cardiac markers of troponins, creatine kinase, myoglobin and lactate dehydrogenase in the diagnosis of type 2 DM subjects with heart diseases symptoms in Yenegoa, Bayelsa State of Nigeria provided reliable information of an impending infarction and other heart diseases. This is as presented in the tables.

4. Discussion

The clinical utility of cardiac markers has been on the increase for decades now and cannot be overemphasized. A growing body of literature supports the diagnostic usefulness of the cardiac troponins as an example, not only to diagnose acute myocardial infarction, but also to provide reliable information about the likelihood of an impending infarction as has been indicated in this study. Diabetes mellitus is associated with different comorbidities, an increased risk of different heart disease, coronary heart disease (CHD), cardiovascular disease (CVD) and stroke with its connected mortality. The assessment of these risk factors and the disease conditions were made possible with the tools of the cardiac markers, that are currently available and that have clinical use as diagnostic, prognostic or predictive biomarkers.

This prevalence study has shown that 14.33% of the studied subjects (**Table 1** and **Table 2**) were diagnosed of different heart disease. It is established however, that diabetes mellitus confers an increased risk for cardiovascular events independent of other traditional risk factors of hypertension and or dyslipedemia [10]. Diabetes mellitus type 2 patients, along with age and duration of illness will impart the risk for developing CVD. The result of the study showed that patients that have suffered the illness for more than 21 and above years had the higher incidence of heart disease with a percentage of 54.90. This is followed by the DM

Table 1. Characteristics of study population.

Characteristic	N	%	95% Confidence Interval	
			Lower	Upper
Sex				
Female	197	55.34	50.14	60.42
Male	159	44.66	39.58	49.86
Duration of Illness (Years)				
0 - 10	135	37.92	32.76	42.78
11 - 20	119	33.43	28.99	38.77
21 and above	102	28.65	24.20	33.56
Mean ± SD	356	14.51	13.74	15.28
Disease Status*				
CVD$^{\epsilon}$	51	14.33	9.20	19.09
No CVD	305	85.67	80.91	90.80

CVD: Cardio Vascular Disease. *Patients with chronic diabetic disease; $^{\epsilon}$Based on samples in which all parameters of interest were measured. The result as shown in Table 1, indicates that 51 (14.33%) of the studies Diabetic Subjects had different heart diseases. At 95% confidence level, this was statistically significant.

Table 2. Association of cardio vascular disease among chronic diabetic patients by sex and duration of illness (in years).

Characteristic	N	Chronic Diabetic Patients		Test Statistics	
		With CVD	Without CVD		
		n (%)	N (%)	X^2 (df)	*p-value*
Sex					
Female	197	29 (8.15)	168 (47.19)		
Male	159	22 (6.18)	137 (38.48)	0.66 (1)	0.045^{ss}
Duration of Illness (Years)					
0 - 10	135	8 (2.25)	126 (35.67)		
11 - 20	119	15 (4.21)	104 (29.21)		
21 and above	102	28 (7.87)	74 (20.79)	27.51 (2)	<0.0001****
Total	356	51 (14.33)	305 (85.67)		

X^2 (df): Chi-square (degree of freedom); CVD: Cardio Vascular Disease. Significance Level: ****$p < 0.0001$; ss = significant ($p < 0.05$). Table 2 results showed that out of the 51 studied subjects with CVD (all parameters measured are positively elevated) 29 (8.15%) were females and 22 (6.18%) were males. The studied subjects with 21 and above year's duration of illness had the highest incidence of 28 (7.87%).

patients group 11 to 20 years with 29.41% (Table 2). This is because the metabolic abnormalities of diabetes cause mitochondrial superoxide over production in endothelia cell of both large and small vessels as well as in the myocardial that leads to complications [4]. From the study, 56.86% of the 14.33% with different heart disease are females irrespective of the fact that 44.66% of the studied type 2 diabetes mellitus patients are males (Table 2). Earlier study has shown that less care for women with risk of developing heart disease has been responsible for higher incidence in women [31].

The reason for this incidence in females is multi factorial and related to a heavier risk factor burden, more involvement of inflammatory factors, smaller vessel size of the coronary arteries and an often less aggressive treatment of diabetes in women [32]. From the study, about 26.12% of the assessed subject has shown evidence of developing CVD. This is as a result of elevation in the serum values of different biomarkers investigated (Table 3). From the study, there is a

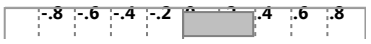
strong positive correlation (Table 4 and Table 5) between the various parameters measured in chronic Diabetes mellitus subjects. It has been suggested [33] that an association between hyperglycaemia and intracellular metabolic changes can result in oxidative stress, low grade inflammation and endothelial dysfunction. Comparison between the Mean ± SEM of the parameters for diagnosis of CVD by sex, duration of diabetic illness and disease status of CVD showed a statistical 1significant value for the duration of illness (Table 6), CVD and non CVD subjects and non-significant value between the gender groups.

Table 3. Mean ± SEM of parameters for diagnosis of cardio vascular disease (CVD).

Parameter	N	Mean ± SEM	*p*-value
Troponin I [CTnl] (ug/L)			
CVD	53	0.714 ± 0.026^{a}	
No CVD	303	0.259 ± 0.009^{b}	<0.0001****
Troponin T [CTnT] (ug/L)			
CVD	51	0.245 ± 0.012^{a}	
No CVD	305	0.048 ± 0.004^{b}	<0.0001****
Myoglobin [MYO] (ug/L)			
CVD	65	158.311 ± 6.388^{a}	
No CVD	291	55.059 ± 2.109^{b}	<0.0001****
Creatin-Kinase [CK – MB] (u/L)			
CVD	59	34.503 ± 2.123^{a}	
No CVD	296	7.177 ± 0.656^{b}	<0.0001****
Total Lactase Dehydrogenase [LDH] (u/L)			
CVD	69	325.897 ± 9.387^{a}	
No CVD	287	145.524 ± 3.293^{b}	<0.0001****

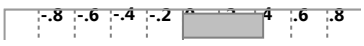
SEM: Standard Error of Mean; CVD: Cardio Vascular Disease; Within parameter, means ± SEM with different superscripts are significantly different at $p < 0.05$. Significance Level: ****$p < 0.0001$. Table 4 results indicated that 59, 53, 65, 51 and 69 diabetes subjects had elevated levels of cTn1, cTnT, Myo, CK-MB and LDH respectively. The values were statistically significant. 51 DM patients had all the parameters measured elevated, while 93 (26.12%) had either one or more of the parameters elevated.

Table 4. Pairwise correlations between measured parameters in chronic diabetic patients with CVD.

Variable	by Variable	Correlation	Lower 95% CI	Upper 95% CI	*p*-value	Graphical Representation
Troponin T (ug/L)	Troponin I (ug/L)	0.3931	0.0451	0.6561	0.0287*	
Myoglobin (ug/L)	Troponin I (ug/L)	0.1794	−0.1869	0.5018	0.3343^{ns}	
Myoglobin (ug/L)	Troponin T (ug/L)	0.5125	0.1932	0.7336	0.0032**	
Creatine-Kinase (u/L)	Troponin I (ug/L)	0.0888	−0.2742	0.4296	0.6347^{ns}	
Creatine-Kinase (u/L)	Troponin T (ug/L)	0.4032	0.0571	0.6629	0.0245*	
Creatine-Kinase (u/L)	Myoglobin (ug/L)	0.8640	0.7345	0.9328	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Troponin I (ug/L)	0.1533	−0.2126	0.4815	0.4104^{ns}	
Total Lactase Dehydrogenase (u/L)	Troponin T (ug/L)	0.6644	0.4056	0.8246	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Myoglobin (ug/L)	0.7314	0.5090	0.8623	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Creatine-Kinase (u/L)	0.8424	0.6958	0.9217	<0.0001****	

CVD: Cardio Vascular Disease. Significance Level: *$p < 0.05$; **$p < 0.01$; ****$p < 0.0001$; ns= Not significant ($p > 0.05$). A strong positive correlation between the measured parameters.

Table 5. Pairwise correlations between measured parameters in chronic diabetic patients without CVD.

Variable	by Variable	Correlation	Lower 95% CI	Upper 95% CI	*p*-value	Graphical Representation
Troponin T (ug/L)	Troponin I (ug/L)	0.4486	0.3571	0.5316	<0.0001****	
Myoglobin (ug/L)	Troponin I (ug/L)	0.3806	0.2835	0.4699	<0.0001****	
Myoglobin (ug/L)	Troponin T (ug/L)	0.6523	0.5849	0.7107	<0.0001****	
Creatine-Kinase (u/L)	Troponin I (ug/L)	0.4135	0.3191	0.4998	<0.0001****	
Creatine-Kinase (u/L)	Troponin T (ug/L)	0.6812	0.6181	0.7355	<0.0001****	
Creatine-Kinase (u/L)	Myoglobin (ug/L)	0.6763	0.6126	0.7313	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Troponin I (ug/L)	0.4256	0.3322	0.5107	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Troponin T (ug/L)	0.5999	0.5253	0.6654	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Myoglobin (ug/L)	0.6265	0.5556	0.6884	<0.0001****	
Total Lactase Dehydrogenase (u/L)	Creatine-Kinase (u/L)	0.6033	0.5292	0.6682	<0.0001****	

CVD: Cardio Vascular Disease. Significance Level: ****$p < 0.0001$. A strong positive correlation between the measured parameters.

Table 6. Mean ± SEM of Parameters for diagnosis of cardio vascular disease (CVD) by sex, duration of diabetic illness and disease status of CVD.

Characteristics	N	Troponin I [CTnl] (ug/L)	Troponin T [CTnT] (ug/L)	Myoglobin [MYO] (ug/L)	Creatine-Kinase [CK – MB] (u/L)	Total Lactase Dehydrogenase [LDH] (u/L)
		Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM	Mean ± SEM
Sex						
Female	197	0.317 ± 0.015	0.068 ± 0.006	62.786 ± 3.470	9.808 ± 0.006	164.793 ± 5.800
Male	159	0.301 ± 0.017	0.064 ± 0.007	68.214 ± 3.862	9.245 ± 1.120	165.893 ± 6.456
Test Statistic p-value		0.465^{ns}	0.713^{ns}	0.296^{ns}	0.709^{ns}	0.899^{ns}
Duration of Illness (Years)						
0 - 10	135	0.256 ± 0.018^{a}	0.045 ± 0.007^{a}	52.129 ± 4.081^{a}	7.240 ± 1.204^{a}	152.246 ± 6.945^{a}
11 - 20	119	0.300 ± 0.019^{b}	0.061 ± 0.008^{b}	64.949 ± 4.313^{b}	9.191 ± 1.273^{b}	162.783 ± 7.339^{b}
21 and above	102	0.388 ± 0.021^{c}	0.099 ± 0.009^{c}	82.703 ± 4.678^{c}	13.031 ± 1.380^{c}	185.355 ± 7.961^{c}
Test Statistic p-value		<0.0001****	<0.0001****	<0.0001****	0.0068**	0.0072**
Disease Status*						
CVD$^{\epsilon}$	51	0.792 ± 0.028^{a}	0.258 ± 0.012^{a}	163.321 ± 6.852^{a}	34.503 ± 2.123^{a}	337.581 ± 11.043^{a}
No CVD	305	0.263 ± 0.009^{b}	0.048 ± 0.004^{b}	55.852 ± 2.116^{b}	7.177 ± 0.656^{b}	148.858 ± 3.411^{b}
Test Statistic p-value		<0.0001****	<0.0001****	<0.0001****	<0.0001****	<0.0001****

DVD: Cardio Vascular Disease; SEM: Standard Error of Mean. nnn *Patients with chronic diabetic disease; $^{\epsilon}$Based on samples in which all parameters of interest were measured; Within parameter, means ± SEM with different superscripts are significantly different at $p < 0.05$. Significance Level: **$p < 0.01$; ****$p < 0.0001$; ns = Not significant ($p > 0.05$).

The suggested mechanisms that can link accelerated atherosclerosis and increased cardiovascular risk in subjects with diabetes are still poorly understood. It has been noted that an association between hyperglycemia and epigenetic factors by different types of reactions could be responsible for the interaction between genes and environment and for this reason account for the association between diabetes and cardiovascular disease [34]. The boxplot in this study result analysis (**Figures 1-5**) has shown the distribution of the different measured parameters variability by cardiovascular diseases. There's a very positive correlation (**Figure 6** and **Figure 7**) which indicate that there's a relationship between the cardiac markers parameters in chronic diabetes with cardiovascular diseases.

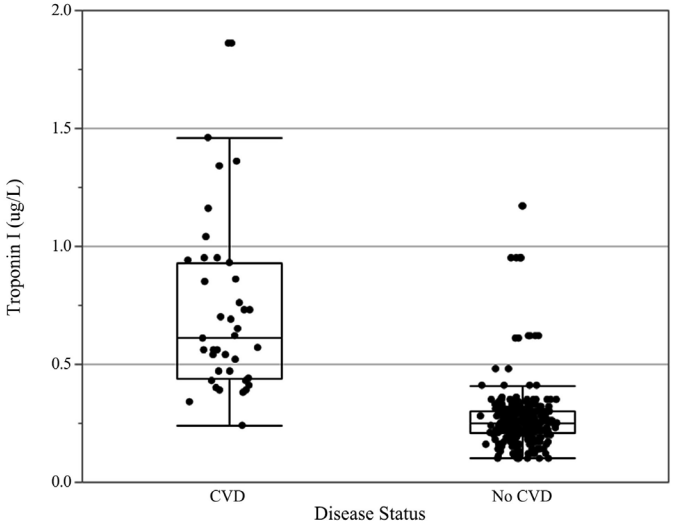


Figure 1. Boxplot of Troponin I (ug/L) by cardio vascular disease (CVD) status.

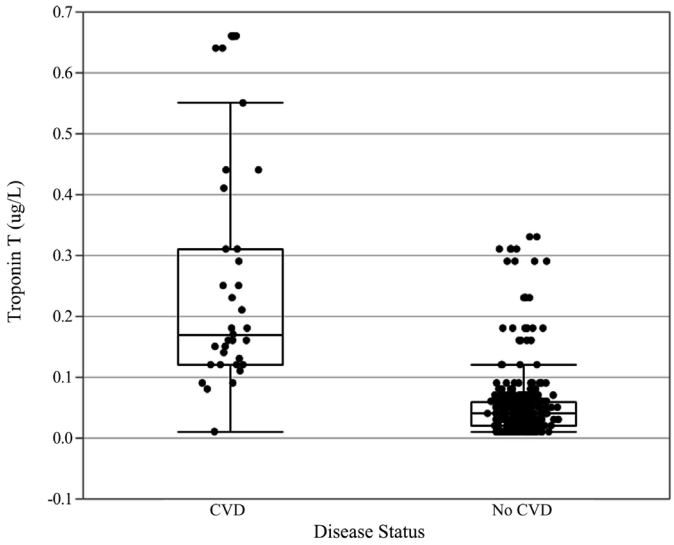


Figure 2. Boxplot of Troponin T (ug/L) by cardio vascular disease (CVD) status.

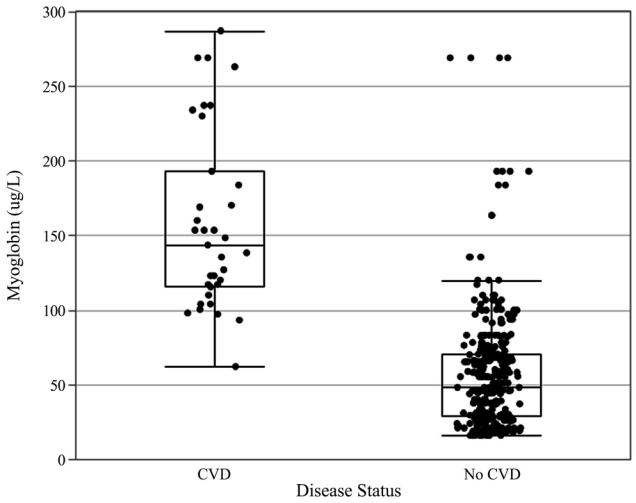


Figure 3. Boxplot of myoglobin (ug/L) by cardio vascular disease (CVD) status.

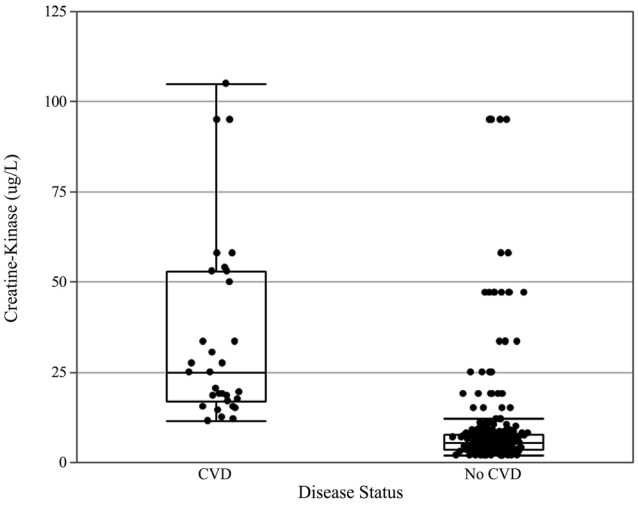


Figure 4. Boxplot of creatine-kinase (u/L) by cardio vascular disease (CVD) status.

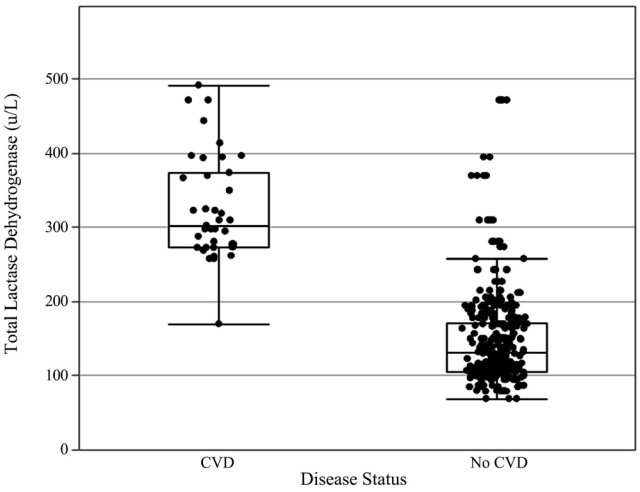


Figure 5. Boxplot of total lactase dehydrogenase (u/L) by cardio vascular disease (CVD) status.

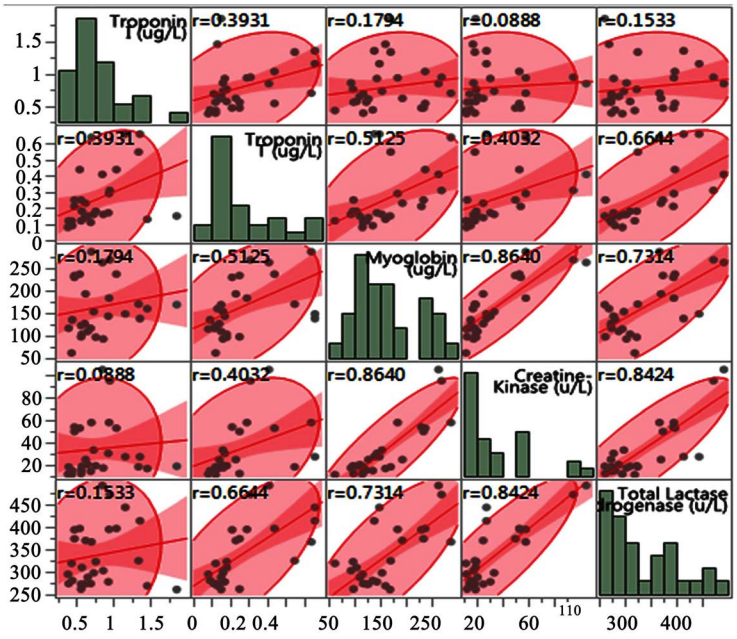


Figure 6. Scatterplot matrix showing the relationships between measured parameters in chronic diabetic patients with cardio vascular disease.

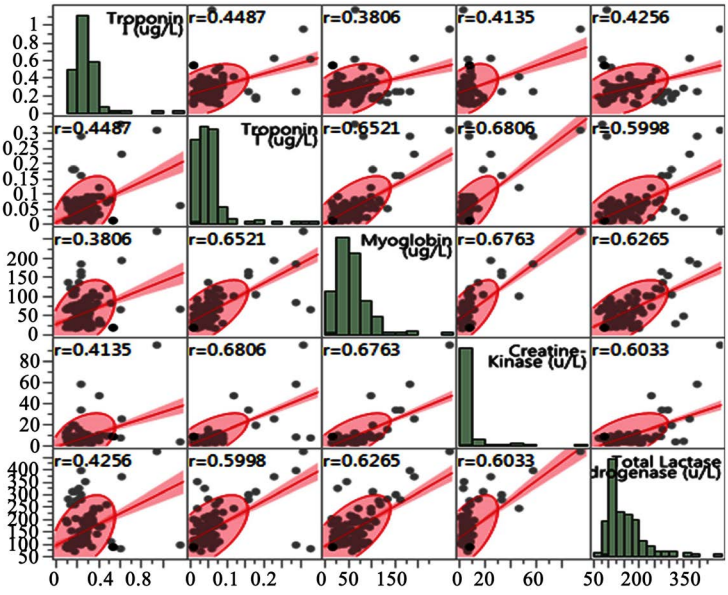


Figure 7. Scatterplot matrix showing the relationships between measured parameters in chronic diabetic patients with no cardio vascular disease.

5. Conclusion

The study sought to evaluate the diagnostic performance of cardiac markers in patients suffering from Diabetes attending the endocrine hospitals. From the study, tools of cardiac markers can be used in the diagnosis/assessment of CVD in type 2 DM patients. The risk of developing CVD is more in females than the male subjects that are suffering from type 2 DM and those with long duration of the illness in Bayelsa State, Niger Delta Region, South of Nigeria.

Acknowledgements

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Limitations of the Study

1) Getting the consent of the identified subjects, as many of them are not literate enough to understand the reasons for the study.

2) The cost of the various cardiac markers kit.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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