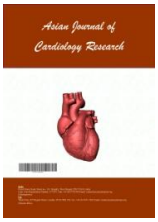

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Alterations in Some Markers of Inflammation and Coagulation in Patients with Heart Failure in South-Eastern Nigeria

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Authors' contributions

This work was carried out in collaboration among all authors. Authors ICI and MNC designed the study, performed the statistical analysis, and wrote the first draft of the manuscript. Authors EJA, OLI and UCV wrote the protocol, managed the analyses of the study and the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Background: Recent studies indicate that inflammation plays a critical role in the pathogenesis of Heart Failure, yet there is scarcity of report on blood markers of inflammation and coagulation in patients with heart failure from a Black-African population like Nigeria.
Objective: The aim of this study is to examine if there is alteration in blood levels of some inflammation and coagulation markers in patients with heart failure in Nigeria.

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Methods: Eighty (80) patients with heart failure participated in this study. They were age-matched with 80 apparently healthy subjects who served as the control subjects. Ten (10) mL of venous blood samples were collected from each participant and dispensed into EDTA, Plain and sodium citrate containers respectively. The samples were used for determination of erythrocyte sedimentation rate) (ESR), C -Reactive Protein (CRP), myoglobin, Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT). IBM SPSS Statistics 21 was used to carry out statistical analysis on the data generated.

Results: There were significant higher levels of APTT (37.33 ± 3.93ng/mL versus 32.05±3.64ng/mL, p=0.000), PT(15.46 ± 7.64 versus 12.17 ± 1.17, p = 0.024), ESR(36.63 ± 34.33 versus 14.66 ± 13.86, p=0.003), Myoglobin(74.72 ± 43.49 versus 35.04 ± 14.07, p=0.000) and CRP (29.24 ± 4.99 versus 16.14 ± 8.64, p=0.000) respectively in all Patients with heart failure compared to controls. There was no significant difference in body mass index (BMI) (28.41 ± 9.88 versus 26.43 ± 1.61, p=0.298) in all patients with heart failure compared to controls. There was a significant positive correlation of CRP with myoglobin (r-0.452, p=0.012) in all patients with heart failure.

Conclusion: Elevated blood levels of inflammation and coagulation markers; CRP, Myoglobin, ESR, APTT and Prothrombin Time, may be associated with heart failure in Nigeria.

Keywords: Heart failure; inflammation; coagulation; CRP; myoglobin; APTT; prothrombin time; Nigeria.

1. INTRODUCTION

Heart failure is the final common pathway to various heart diseases. It is a costly and potentially fatal clinical syndrome characterized by dyspnea, fatigue, swollen legs and signs of congestion leading to frequent hospitalizations, poor quality of life and shortened life expectancy [1,2]. This condition occurs when the heart is unable to pump sufficiently to maintain adequate blood flow to meet the body's need [3], consequently the increase of pressure in heart chambers to maintain an adequate blood flow Heart failure is the leading cause of death globally with more than 26 million people affected annually [4]. It has been previously reported that 45% of patients die from heart failure due to hypertension [5].

Predisposing factors to chronic heart failure include degenerative valvular heart disease, coronary heart disease, a previously myocardial infarction, high blood pressure, rheumatic heart disease, atrial fibrillation, cardiomyopathy of unknown cause, excess alcohol, physical inactivity, cigarette smoking, overweight, diabetes, infections and male population [5,6]. Complications of heart failure include pulmonary pneumonia, stroke, organ failure, kidney failure, weight loss, lethargy, weakness and sudden death. Previous report from Nigeria indicates that hypertension and rheumatic heart disease are the main causes of heart failure in this environment [7].

There has been increase in documentation of the important role of inflammation in the pathogenesis of heart failure [8,9,10]. Inflammation and heart failure are strongly interconnected and mutually reinforce each other [11,12], therefore, positioning inflammation to be a vital therapeutic target for the treatment of heart failure [13,14]. Significant correlations of elevated serum concentrations of pro-inflammatory cytokines and adverse clinical outcomes has been observed for heart failure patients [15,16,17].

Markers of inflammation include C-Reactive Protein (CRP), Myoglobin, Troponin, Cytokins, interleukins and ESR [18]. ***C-reactive protein (CRP)*** is a substance produced by macrophages in the liver and adipocytes in response to inflammation, and is integrated in the acute phase response pathway. Raised CRP level may forecast myocardial infarction, stroke and vascular death in several situations [19,20]. It is a non- specific marker of inflammation, but a better marker for acute reaction than ESR. While a combination of ESR and CRP levels may correlate with the degree of inflammation [2].

Myoglobin is a small protein found in the heart and skeletal muscles. It is the primary oxygen carrying pigment of muscle tissue [21]. It traps oxygen in the muscle to allow muscle cells work properly and is released from damaged muscle tissue, filtered by the kidneys, and transported to the renal tubular epithelium and so may cause acute kidney injury [22]. Myoglobin is a sensitive

marker for muscles injury, making it a potential marker for heart attack [23]. In human, myoglobin is only found in the bloodstream after muscle injury [24] It is an abnormal finding, and can be diagnostically relevant when found in blood.

Erythrocytes Sedimentation Rate (ESR) is non-specific measure of inflammation. It may be raised in a wide range of infectious, inflammatory, degenerative and malignant conditions associated with changes in plasma protein; particularly increases in fibrinogen, Immunoglobins and C-Reactive proteins [2].

Coagulation also known as clotting, is a process by which blood changes from liquid to gel, forming a blood clot, which potentially results in haemostatic cessation of blood loss from a damaged vessel followed by repair. Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) are important clinical coagulation tests which measure integrated actions of majority of coagulation factors in extrinsic and intrinsic pathways of coagulation cascade of blood [25,26].

Heart failure is increasingly becoming a major cause of hospital attendance and morbidity globally and locally in Nigeria. Despite indications that alterations in CRP level, which is an inflammatory marker may be associated with this disorder [27,28,29], it has not been adequately investigated in Nigerian population. Besides, there is inadequate report on the association of other inflammatory markers with coagulation markers in the prognosis of heart failure particularly in a black African population like Nigeria. This study therefore seems be the first report from a Nigerian population to bridge this gap in knowledge.

2. MATERIALS AND METHODS

2.1 Study Area

This study was carried out in the Cardiology Unit, University of Nigeria Teaching Hospital (UNTH), Ituku-Ozalla, Enugu, Nigeria. This tertiary Hospital serves as referral hospital for treatment of serious ailment cases from Enugu state and neighboring South-Eastern states of Nigeria.

2.2 Study Population

By random sampling technique, 80 patients with heart failure consisting of 40 males and 40 females were enrolled for this study with the help of Consultant Cardiologist. The patients were between the ages of 45 and 75 years. they were age-matched with 40 apparently healthy males and 40 apparently healthy females respectively, who served as the control subjects.

2.3 Selection Criteria

2.3.1 Inclusion criteria for patients with heart failure

The inclusion criteria for Heart failure are based on at least 2 major clinical criteria, or 1 major clinical criterion with 2 minor clinical criteria [30].

2.3.2 Major criteria for the clinical diagnosis of heart failure

Left ventricle Ejection fraction less than 40%, paroxysmal nocturnal dyspnea orthopnea, neck-vein distension, rales, cardiomegaly on chest x-ray, acute pulmonary edema, S3 gallop, increased venous pressure >16cm of water, increased circulation time > 25s, and hepatojugular reflux,

2.3.3 Minor criteria for the clinical diagnosis of heart failure

ankle edema, night cough, dyspnea on exertion, hepatomegaly, pleural effusion, and vital capacity decreased 1/3 from maximum tachycardia (rate of >120 per min).

2.3.4 Exclusion criteria for patients with heart failure

Exclusion criteria are as follows: Patients with rheumatological and neoplastic disease because they can alter markers of inflammation**,** other chronic diseases like diabetes mellitus, AIDS, tuberculosis and hepatitis. Subjects with absence of clinical manifestation of heart disease, and patients who did not give inform consent for the study.

2.4 Study Design

The period of subjects' enrolment, classification, sample collection, laboratory determination and data analysis lasted between. A structured questionnaire was administered to all the subjects to obtain their Sociodemographic features.

2.5 Sample Collection and Laboratory Analysis

About 10 mL of venous blood each was collected from Patients with Heart Failure and Control Subjects. About 3.5mL of the sample was dispensed into a plain tube and allowed to clot to obtain serum for C-RP and Myoglobin determination. while 2mL of blood was dispensed into EDTA and mixed for ESR analysis. Also 4.5 mL was also dispensed into 0.5mL of 3.13% trisodium citrate sample container, then centrifuged at 4000rpm for 15 minutes to obtain platelet-poor plasma for APTT and PT determination. All the specimens were stored refrigerated at 2-8 ^{o}C. ***Myoglobin*** and ***C-Reactive Protein*** were determined using ELISA technique employing Accu-Bind test kit code no: 3225- 300 (MonoBind Inc, USA) and Accu-Bind ELISA kit code no-3125-300 (MonoBind, USA) respectively. ESR was determined using Westergren's method. Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) were analyzed using Sysmex CA-104 Semi auto blood Coagulation analyzer (Sysmex, Germany.), employing APTT reagent kit Cat No 100207 (Giesse Diagnostics, Italy) and PT reagent kit Cat No 100107 (Giesse Diagnostics, Italy) respectively.

2.6 Statistical Analysis

All data generated in this study were subjected to statistical analysis employing IBM SPSS Statistics 21 to determine Mean, Standard Deviation, Students' t-test and Pearson's Correlations. Results were considered statistically significant at $p<0.05$, and expressed as Mean ±SD.

3. RESULTS

3.1 Some Markers of Inflammation, Coagulation Parameters and BMI in All Patients with Heart Failure Versus Controls

There were significant higher levels of APTT, PT, ESR, Myoglobin and CRP (p=0.000, p = 0.024, p=0.003, p=0.000 and p=0.000 respectively) in all patients with heart failure compared to all controls. There was no significant difference in the level of BMI (p=0.298) in all Patients with Heart Failure compared to all Controls (Table 1).

3.2 Some Markers of Inflammation, Coagulation Parameters and BMI in Male Patients with Heart Failure Versus Male Controls

There were significant higher levels of APTT, PT, ESR, Myoglobin and CRP (p=0.000, p=0.006, p=0.000, p=0.000 and p=0.000 respectively) in Male Patients with Heart Failure compared to Male Controls. But there was no significant difference in the level of BMI (p=0.170) in Male Patients with Heart Failure compared to Male Controls (Table 2).

3.3 Some Markers of Inflammation, Coagulation Parameters and BMI in Female Patients with Heart Failure Versus Female Controls

There were significant higher levels of APTT. PT, ESR, Myoglobin, and CRP (p=0.000, p=0.005, p=0.013, p=0.008 and p=0.000 respectively) in Female Patients with Heart Failure compared to the Female Controls. There was no significant difference in level of BMI (p=0.437) in Female Patients with Heart Failure when compared with the Controls (Table 3).

3.4 Some Markers of Inflammation, Coagulation Parameters and BMI in Male Patients with Heart Failure Versus Female Patients with Heart Failure

There were no significant differences in the levels of APTT, PT, Myoglobin, CRP and BMI (p= 0.509, p=0.127, p=0.567, p=0.685 and p=0.603 respectively) in Male Patients with Heart Failure when compared with the Female Patients with Heart Failure. There was significantly lower ESR (p=0.034) level in Male Patients with Heart Failure when compared with Female Patients with Heart Failure (Table 4).

3.5 Correlation of Serum CRP with Myoglobin, APTT, PT, ESR and BMI in All Patients with Heart Failure

There was a significant positive correlation of serum CRP with Myoglobin (r=0.452 & p=0.012), while there were no significant correlations of serum CRP with APTT, PT, ESR and BMI (r=0.037 & P=0.846, r=0.244 & P=0.194, r=0.104 & P=0.504, r=0.348 & P=0.059 respectively) in All Patients with Heart Failure (Table 5).

Table 1. Some markers of inflammation, coagulation parameters and BMI in all patients with heart failure versus controls

VARIABLES (Mean ± SD)	All-Patients with Heart Failure (n-40)	All-Controls (n=40)	t-value	p-value
APTT (sec)	37.33 ± 3.93	32.05±3.64	6.555	0.000
PT (sec)	15.46 ± 7.64	12.17 ± 1.17	2.386	0.024
ESR (mm/hr)	36.63 ± 34.33	14.66 ± 13.86	3.261	0.003
Myoglobin (ng/ml)	74.72 ± 43.49	35.04 ± 14.07	5.798	0.000
CRP (ng)	29.24 ± 4.99	16.14 ± 8.64	9.423	0.000
`BMI	28.41 ± 9.88	26.43 ± 1.61	1.060	0.298

Table 2. Some markers of inflammation, coagulation parameters and BMI in male patients with heart failure versus male controls

VARIABLES (Mean ± SD)	Male Patients With Heart Failure (n=40)	Male Controls (n=40)	t-value	p-value
APTT (sec)	36.39 ± 3.94	32.32±3.00	4.363	0.000
PT (sec)	16.21 ± 8.86	12.30 ± 0.72	2.886	0.006
ESR (mm/hr)	29.36 ± 25.81	10.44 ± 7.73	4.084	0.000
Myoglobin (ng/ml)	79.41 ± 16.26	34.53 ± 15.23	8.667	0.000
CRP (ng)	29.58 ± 4.97	17.25 ± 7.05	6.258	0.000
BMI	28.21 ± 8.62	26.22 ± 1.38	1.398	0.170

Table 3. Some markers of inflammation, coagulation parameters and BMI in female patients with heart failure versus female controls

VARIABLES (Mean ± SD)	Female Patients with Heart failure (n=40)	Female Controls (n=40)	t-value	p-value
APTT (sec)	38.94±3.52	31.6±4.68	5.583	0.000
PT (sec)	14.02 ± 2.86	11.97 ± 1.82	3.145	0.005
ESR (mm/hr)	49.18 ± 42.67	23.72 ± 19.66	2.725	0.013
Myoglobin (ng/ml)	70.67 ± 57.78	35.48 ± 13.35	2.929	0.008
CRP (ng)	28.90±5.10	15.03 ± 10.04	5.672	0.000
BMI	28.76 ± 11.77	26.62± 1.92	0.792	0.437

Table 4. Some markers of inflammation, coagulation parameters and BMI in male patients with heart failure versus female patients with heart failure

Variable (Mean±SD)	Male Patients with Heart Failure (n-40)	Female Patients with Heart Failure (n=40)	t-value	p-value
APTT (sec)	36.39 ± 3.94	38.94±3.52	-0.689	0.509
PT (sec)	15.65±9.85	14.02±2.84	1.566	0.127
ESR (mm/hr)	29.36±25.81	46.31±42.38	-2.204	0.034
Myoglobin (ng/ml)	81.35±14.30	72.46± 63.49	0.585	0.567
CRP (ng)	29.58±4.97	28.90±5.10	0.412	0.685
BMI	28.21±8.62	29.53±12.21	-0.524	0.603

Table 5. Correlation of serum CRP with Myoglobin, APTT, PT, ESR and BMI in all patients with heart failure

Dependent Variables	N	r- value	p-value
Myoglobin	40	0.452*	0.012
APTT (sec)	40	0.037	0.846
PT (sec)	40	0.244	0.194
ESR (mm/hr)	40	0.104	0.504
BMI	40	0.348	0.059

4. DISCUSSION

Data from this present study showed significantly higher level of markers of inflammation; CRP, myoglobin and ESR in Heart failure patients compared to the Controls. It appears that inflammation is critical in the development and evolution of atherosclerosis [29], and thus heart failure; from the establishment of the atherosclerotic lesion triggered by lipid deposition, till rupture of fat plaques [29]. At the onset of inflammatory response, there is advance of an interface amid, inflammatory cells, plasma lipoproteins and the vascular wall, with the release of numerous adhesion molecules and cytokines. In addition to this, acute phase markers including CRP, ceruloplasmin, fibrinogen, are produced [31]. Previous studies have implicated these markers as predictors of cardiovascular disease [32].

In animal models, CRP has been found to significantly increase infarct size, hence a growing evidence that CRP is not only a marker for cardiovascular disease but also might be pathogenic [33]. Production of CRP, in addition to rise in level of other pro-inflammatory cytokines begins during the first phase of the inflammatory process, thus establishing its role as a risk marker in this process. Furthermore, CRP causes instability of vascular endothelium by inhibiting NO production, inducing LDL oxidation by enabling LDL entrance in the macrophage, and contributes in destabilization of the fibrous layer of the atheroma. This destabilization is triggered via the stimulus of matrix methaloproteinase-1, released with collagen and other proteins degradation, inducing thrombus formation in the endothelial wall and therefore increasing the risk of cardiovascular events [32], and consequently heart failure.

The findings in our present study is consistent with a very recent report that patients with chronic heart failure, have an elevated plasma CRP that is associated with increase in congestion and a worse prognosis [34] Previous studies propose that chronic heart failure may be an inflammatory disease, and it has been documented that proinflammatory cytokines such as TNF and interleukin-6 are significantly raised in such patients [15,35] Increased CRP has also been reported to be an independent predictor of incident Chronic Heart Failure in a community-based elderly population [36].

Myoglobin is released from a damaged muscle tissue and may result to inflammation, heart attack, [23] and consequently heart failure. Therefore, the higher level of myoglobin observed in both male and female heart failure patients may be due to muscle injury. It has been previously noted that exercise intolerance of chronic heart failure patients with normal hematocrit is not as a result of myoglobin shortage in locomotor muscle fibers [37]. Altered myoglobin by itself is a critical influence that controls relative utilization of fatty acid versus glucose, hence placing myoglobin in a vital stage within the regulatory system that controls cardiac energy production [38]. The possibility of function of myoglobin has been much extended beyond O_2 storage and distribution to comprise a critical role in moderating the cytosolic levels of the key signaling molecule nitrogen oxide (NO) [39].

Conditional to its oxygenation state, myoglobin possibly will not only function as a NO scavenger but as well through its nitrite reductase action as a NO producer, thus reversibly adjusting mitochondrial respiration to the tissue's O_2 tension. Study of these $myo^{-/-}$ species showed that the dynamic association amongst myoglobin and NO plays a vital role equally in physiological and pathological conditions, like hypoxia and ischemia/reperfusion [39].

However, the no significant difference in level of myoglobin observed in male patients with heart failure compared to female patients with heart failure in the present study indicate that it may

not be gender dependent in patients with heart failure.

ESR confirms the presence or absence of inflammatory activity in the body [40]. The higher levels of ESR observed in Patients with Heart failure may suggest the presence of inflammatory condition which is associated with changes in plasma protein, clothing protein and increase in fibrinogen [2]. This increase could also serve as indices for evaluating hemostatic abnormalities in patients with heart failure and also a guide for treatment of heart failure.

The higher levels of coagulation markers; Activated Partial Thromboplastin Time (APTT) and Prothrombin Time (PT) observed in heart failure patients may be due to endothelial damage as a result of atherosclerosis probably caused by hypertension that resulted to heart failure. Endothelial damage and platelet activation are involved in coagulation and fibrinolytic system [41]. Timely assessment of these coagulation markers is important as to avert coagulation disorders and hemostatic aberrations in patients with heart failure to prevent life threatening events. Previous study from Nigeria reported significant increases in the prothrombin time and activated partial thromboplastin time of hypertensive patients when compared to those of the normotensives [42].

Findings in this study indicate that changes in BMI may not be associated with heart failure in this environment. Previous studies have reported that lower BMI (normal weight range) was associated with increased age, worsened heart failure and increased risk of death [43].

Evaluation of a single biomarker might not reflect the complex interactions in heart failure, but using a multi-marker approach is more suitable for this purpose [44]. Thus, determination of levels of inflammatory and coagulation markers may be appropriate.

We suggest that Monoclonal antibodies such as tocilizumab (TCZ) and sarilumab and humanized TNF-α-inhibitors, namely adalimumab and infliximab [45], may be used to regulate the increase in markers of inflammation observed in the heart failure patients. Nevertheless, recent literature emphasis the role of low testosterone in cardiovascular disease, therefore the need for testosterone replacement in symptomatic elderly male heart failure patients with low testosterone levels [46].

5. CONCLUSION

Unlike BMI, higher blood levels of inflammation and coagulation markers; CRP, Myoglobin, ESR, APTT and Prothrombin Time may be associated with incidence of heart failure in Nigeria.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

ETHICAL APPROVAL AND CONSENT

The study protocol was approved by the University of Nigeria Teaching Hospital Enugu Health Research Ethics Committee with reference number *UNTH/CSA/329/VOL5.* Written *informed consent* was obtained from all study participants prior to their enrolment and collection of blood samples in accordance with the "*1964 Helsinki declaration" and its later amendments in 2000.*

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. McMurray JJV, Pfeffer MA. Heart failure. Lancet. 2005;365(9474):1877-89.
2. Bray C, Bell LN, Liang H, Haykal R, Kaiksow F, Mazza JJ, et al. Erythrocytes sedimentation rate and C-Reactive Protein measurement and their relevance in clinical Medicine. Wisconsin Medicine Journal. 2016;115(6):317-321.
3. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. ESC Scientific Document Group. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The task force for the diagnosis and treatment of acute and chronic heart failure of the European society of cardiology (ESC) developed with the special contribution of the heart failure association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-2200.

4. Steinberg BA, Zhao X, Heidenreich PA, Peterson ED, Bhatt DL, Cannon CP, et al. Trends in patients hospitalized with heart failure and preserved left ventricular ejection fraction: Prevalence, therapies, and outcomes. Circulation. 2012; 126(1):65-75.
5. Ogah OS, Sliwa K, Akinyemi JO, Falase AO, Stewart S. Hypertensive heart failure in Nigerian Africans: Insights from the Abeokuta Heart Failure Registry. J Clin Hypertens (Greenwich). 2015;17(4): 263-72.
6. He J, Ogden LG, Bazzano LA, Vupputuri S, Loria C, Whelton PK. Risk factors for congestive heart failure in US men and women: NHANES I epidemiologic follow-up Study. Arch Intern Med. 2001;161(7): 996–1002.
7. Onwuchekwe AC, Asekomeh GE. Pattern of heart failure in Nigerian Teaching Hospital. Vascular Health Risk Management. 2009;**5**:745-750.
8. Westermann D, Lindner D, Kasner M, Zietsch C, Savvatis K, Escher F, et al. Cardiac inflammation contributes to changes in the extracellular matrix in patients with heart failure and normal ejection fraction. Circ Heart Fail. 201;4: 44-52.
9. Paulus WJ, Tschope C. A novel paradigm for heart failure with preserved ejection fraction: Comorbidities drive myocardial dysfunction and remodeling through coronary microvascular endothelial inflammation. J Am Coll Cardiol. 2013; 2362(4): 263-71.
10. Libby P, Nahrendorf M, Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded cardiovascular continuum. J Am Coll Cardiol. 2016;67: 1091-103.
11. Dick SA, Epelman S. Chronic heart failure and inflammation: What do we really know? Circ Res. 2016;119:159-176.
12. Van Linthout S, Tschope C. Inflammation-cause or consequence of heart failure or both? Curr Heart Fail Rep. 2017;14(4): 251-265.
13. Heymans S, Hirsch E, Anker SD, Aukrust P, Balligand JL, Cohen-Tervaert JW, et al. Inflammation as a therapeutic target in heart failure? A scientific statement from the translational research committee of the heart failure association of the European society of cardiology. Eur J Heart Fail. 2009;11(2):119-129.
14. Ridker PM, Luscher TF. Anti-inflammatory therapies for cardiovascular disease. Eur Heart J. 2014;35:1782-1791.
15. Torre-Amione G, Kapadia S, Benedict C, Oral H, Young JB, Mann DL. Proinflammatory cytokine levels in patients with depressed left ventricular ejection fraction: A report from the Studies of Left Ventricular Dysfunction (SOLVD). J Am Coll Cardiol. 1996;27:1201-6.
16. Vasan RS, Sullivan LM, Roubenoff R, Dinarello CA, Harris T, Benjamin EJ, et al. Framingham Heart S. Inflammatory markers and risk of heart failure in elderly subjects without prior myocardial infarction: The Framingham Heart Study. Circulation. 2003;107:1486–1491.
17. Edelmann F, Holzendorf V, Wachter R, Nolte K, Schmidt AG, Kraigher-Krainer E, et al. Galectin-3 in patients with heart failure with preserved ejection fraction: Results from the Aldo-DHF trial. Eur J Heart Fail. 2015;17:214-223.
18. Ballantyne CM, Nambi V. Markers of inflammation and their clinical significance. Atheroscler. 2005;6(2):21-29.
19. Ridker PM, Hennekens CH, Buring JE, Buring JE, Rifai N. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. N Engl J Med. 2000;342:836-43.
20. Ridker PM, Stampfer MJ, Rifai N. Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. JAMA. 2001;285(19):248-5.
21. Ordway GA, Garry DJ. Myoglobin: An essential hemoprotein in striated muscle. Journal of experimental Biology. 2004;207(20):3441-3446
22. Naka T, Jones D, Baldwin I, et al. Myoglobin clearance by super high-flux hemofiltration in a case of severe rhabdomyolysis: A case report. Crit Care. 2005;9(2):R90-R95.
23. Weber M, Rau M, Madlener K, Elsaesser A, Bankovic D, Mitrovic V, Hamm C. Diagnostic utility of new immunoassays for the cardiac markers cTnI, myoglobin and CK-MB mass. Clin Biochem. 2005;38(11): 1027-30.

24. Brancaccio P, Lippi G, Maffulli N. Biochemical markers of muscular damage. Clinical Chemistry and Laboratory Medicine. 2010;48(6):757-67
25. Miljic D, Miljic P, Doknic M, Dolnic M, Pekic S, Djurovic M, et al. Changes in prothrombin and activated partial thromboplastin time during replacement therapy with human recombinant growth hormones in growth hormones deficient adults. Hormones (Athens). 2006;5(3): 187-191.
26. Abdollabi A, Shoar N, Shoar S, Rasoulinejad M. Extrinsic and intrinsic coagulation pathway, fibrinogen serum level and platelet count in HIV positive patients, Acta Med Iran. 2013;51(7): 472-476.
27. Wen-Pin Huang, Wei-Hsian Yin, Hsu-Lung Jen, Meng-Cheng Chiang, An-Ning Feng and Mason Shing Young. C-Reactive protein levels in chronic congestive heart failure. Acta Cardiol Sin. 2004;20:7-14
28. Silva D, Lacerda AP. Proteína C reativa de alta sensibilidade como biomarcador de risco na doença coronária. Revista Portuguesa de Cardiologia 31:733-745
29. Hajsadeghi S, Chitsazan M, Chitsazan M, Salehi N, Amin A, Maleki M, et al. Changes of high sensitivity C-reactive protein during clopidogrel therapy in patients undergoing percutaneous coronary intervention. Res Cardiovasc Med. 2015;5:e28997.
30. Adedapo AD. Rising trend of cardiovascular diseases among South-Western Nigerian female patients. Nig J Cardiol. 2017;14:71-4.
31. Cozlea DL, Farcas DM, Nagy A, Keresztesi AA, Ramona Tifrea, Cozlea L, et al. The impact of C-reactive protein on global cardiovascular risk on patients with coronary artery disease. Curr Health Sci J. 2013;39(4):225-231.
32. Cardoso IL, Paulos AT. C Reactive Protein and Cardiovascular Diseases. Int Arch Cardiovasc Dis. 2017;1:003.
33. Stumpf C, Sheriff A, Zimmermann S, Schaefauer L, Schlundt C, Raaz D, et al. C-reactive protein levels predict systolic heart failure and outcome in patients with first ST-elevation myocardial infarction treated with coronary angioplasty. Arch Med Sci. 2017;13(5):1086-1093.
34. Pellicori P, Zhang J, Cuthbert J, Urbinati A, Shah P, Kazmi S, et al. High-sensitivity C-reactive protein in chronic heart failure: Patient characteristics, phenotypes, and mode of death. Cardiovasc Res. 2020;116(1):91-100.
35. Mann DL, Young JB. Basic mechanisms in congestive heart failure. Recognizing the role of proinflammatory cytokines. Chest.1994;105(3):897-904.
36. Gottdiener JS, Arnold AM, Aurigemma GP, Polak JF, Tracy RP, Kitzman DW, et al. Predictors of congestive heart failure in the elderly: The Cardiovascular Health Study. J Am Coll Cardiol. 2000;35(6):1628-37.
37. Bekedam MA, van Beek-Harmsen BJ, van Mechelen W, Boonstra A, van der Laarse WJ. Myoglobin concentration in skeletal muscle fibers of chronic heart failure patients. J Appl Physiol (1985). 2009;107(4):1138-1143.
38. Flogel U, Laussmann T, Gödecke A, Abanador N, Schäfers M, Fingas CD, et al. Lack of myoglobin causes a switch in cardiac substrate selection. Circulation Research. 2005;96:e68–e75.
39. Flogel U, Fago A, Rassaf T. Keeping the heart in balance: The functional interactions of myoglobin with nitrogen oxides. Journal of Experimental Biology. 2010;213:2726-2733.
40. Harrison M. Erythrocyte sedimentation rate and C-reactive protein. Aust Prescr. 2015;38(3):93-94.
41. Kamal AH, Tefferi A, Pruthi RK. How to interpret and pursue an abnormal prothrombin time, activated partial thromboplastin time, and bleeding time in adults. Mayo Clin Proc. 2007;82(7):864-73.
42. Nnamani NA, Emeribe AU, Nasiru IA, Babayo A, Uko EK. Evaluation of prothrombin time and activated partial thromboplastin time in hypertensive patients attending a tertiary Hospital in Calabar, Nigeria. Advances in Hematology. 2014;2014:932039.
43. Shah R, Gayat E, Januzzi JL Jr, Sato N, Cohen-Solal A, DI Somma S, et al. GREAT (Global Research on Acute Conditions Team) Network. Body mass index and mortality in acutely decompensated heart failure across the world: A global obesity paradox. J Am Coll Cardiol. 2014;63(8):778-85.
44. Gencer B, Bonomi M, Adorni MP, Sirtori CR, Mach F, Ruscica M. Cardiovascular risk and testosterone – from subclinical atherosclerosis to lipoprotein function to

heart failure. Rev Endocr Metab Disord. 2021;22:257–274.

45. Rabaan AA, Al-Ahmed SH ,Muhammad J, Khan A, Sule AA, Tirupathi R. et al., Role of inflammatory cytokines in COVID-19 patients: A review on molecular mechanisms, immune functions, immunopathology and immunomodulatory drugs to counter cytokine storm. Vaccines. 2021;9(5):436.

46. Saenz-Pipaon G, Martinez-Aguilar E, Orbe J, Miqueo GA, Fernandez-Alonso P, Paramo JA, et al. The role of circulating biomarkers in peripheral arterial disease. Int J Mol Sci. 2021;22(7): 3601.

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