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Assessing the diagnostic value of CRP, troponin, BNP, and CK-MB in heart disease patients in Iraq

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Abstract
Background: Cardiovascular diseases are among the most widespread diseases around the world that lead to death. Studying inflammatory and cardiac biomarkers reveals new insights into reducing the risk of infection and helping in early diagnosis.
Aims of the study: Evaluating the relationship between cardiac and inflammatory indicators and their relationship to the severity of cardiovascular disease.
Methodology: A case-control study included 50 samples from patients with heart disease diagnosed according to the inclusion criteria and 25 samples from healthy controls. The study was conducted with the approval of the Ethics Committee at the College of Medicine at Al-Nahrain University at Al-Nasiriyah Heart Hospital in Thi-Qar, Iraq, between 1/3/2022 and 1/3/2023. Patients' data were recorded, 5 ml of blood was drawn, and then the serum was separated and stored at -20 °C. Troponin, CRP, CKMP, and BNP levels were measured using an ELISA device.
Result: The study found that there were no statistically important changes in age or body mass index between the control group and the patient group. The amounts of CRP, troponin, BNP, and CK-MB were much higher in people with heart disease compared to healthy controls. The results showed that there were positive links between age and CK-MB and BNP. However, there were no statistically significant links between age and CRP or troponin. An interesting thing about CRP is that it correlated positively with CK-MB but not with troponin or BNP.
Conclusions: The study showed that CRP, troponin, BNP, and CK-MB levels were significantly higher in heart patients compared to healthy controls, reflecting inflammation and myocardial damage. BNP and CK-MB levels were also associated with increasing age. These results support the importance of monitoring these biomarkers for heart disease diagnosis and early medical intervention.

Keywords: Cardiovascular diseases, cardiac troponin, natriuretic peptides, creatine kinase myocardial band, c-reactive protein

Introduction
Heart diseases like coronary and ischemic heart diseases, acute heart failure, peripheral arterial diseases, deep vein or artery thrombosis, pulmonary embolism (PE), and cerebrovascular diseases kill more people than any other disease in the world [1]. Many CVDs might be avoided if they are caught early. This is possible by changing risk factors like smoking, not being active, being overweight, having diabetes, high blood pressure, and cholesterol problems. This is why it's important to have good tools for screening, diagnosing, and making predictions. It's becoming clearer that biomarkers are very important in this area. Aronson *et al*. defined a biomarker as a "biological observation that stands in for and ideally predicts a clinically relevant endpoint or intermediate outcome that is harder to observe [3]. A biomarker is also a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention" [4, 5]. This definition comes from the National Institutes of Health Consortium. So, differences in biomarkers show whether something is healthy or sick, and they may also show how well a treatment is working. In a broad sense, biomarkers are things that can be used to measure things like chemicals, proteins, and genetic factors [3]. More generally, imaging methods used to find and study biological processes that aren't working right are also biomarkers [6]. Heart troponins (cTn), troponin I (cTnI), troponin T (cTnT), and troponin C (cTnC) make up the troponin complex. The complex is made up of three governing proteins.

These parts of the thin strands in cardiac muscle (actin protein) are very important. They help control heart muscle activity, like the amount of calcium inside cells, when the heart contracts and relaxes [7]. TnC is made by both heart muscle cells and slow skeletal myocytes [8]. Heart muscle cells are the only ones that can change TnI and TnT into cardiac forms [9]. Both versions are made in higher amounts during human fetal growth. By the ninth month after birth, they are only found in the heart [10]. So, both TnI and TnT seem like the best ways to study heart problems. Heart cells called cardiomyocytes release a group of proteins called natriuretic peptides (NPs). In many ways, they protect the circulatory system, such as by making you pee more, lowering your salt levels, and making your blood vessels wider. On top of that, they fight the effects of the aldosterone-renin system [11]. Natriuretic peptides can also change the way your metabolism works, which can help you lose weight, break down fat, and make your body more sensitive to insulin [12]. Heart problems like HF, atrial fibrillation, systemic artery hypertension, and inflammatory heart diseases are linked to NPs that aren't working right. So, they are used as biomarkers to learn how CVDs start, how to identify them, how to treat them, and how likely it is that the person will get better [12, 13]. The main NPs in the heart are human atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) [13]. They are part of a regulatory system that works well together, and their structures are similar but not the same in terms of power [14]. The creatine kinase myocardial band (CK-MB) is a different form of the creatine kinase enzyme (CK). It was the best way to find and keep an eye on heart damage in the 1980s [15]. On the inside of cells, CK turns creatine and ATP into creatine phosphate and ADP. Cells that need a lot of energy sometimes need to keep the balance of energy in their bodies. This process can go both ways [16]. This substance, CK-MB, is found in the heart and comes in two forms: CK-MB1 is found in plasma and CK-MB2 is found in tissues [17]. CK-MB is also found in skeletal muscles, though not as much as it is in the heart. [18]. Because of this, CK-MB is a marker for the heart and can be found in higher amounts in the blood when the myocardium is damaged, such as by ischemia or necrosis [19]. When the amount of CK-MB in the blood goes above the upper reference limit for the 99th percentile, it means that the heart muscle is the source of the trouble [20]. People who have had an acute myocardial infarction (MI) can often find high levels of CK-MB three to four hours after the event [21]. These levels are used to help identify MI. In 24 hours, the blood concentration rises, and between 24 and 72 hours, it goes back to normal [22]. When lab tests are done on CK-MB levels, they only show the sum of CK-MB1 and CK-MB2 [23]. Endothelial cells get damaged by inflammation, which also causes arterial plaques to grow. It is one of the main reasons why CVD starts and gets worse. There are times when inflammation can be good and times when it can be bad after a MI. It can help the infarct heal and change its shape, but if it goes on for too long, it can make the infarct bigger and take longer for the heart to recover [24]. A lot of information from well-done studies on both people and animals shows that inflammation is a main cause of circulatory diseases and high blood pressure [25]. C-reactive protein (CRP) is a testable protein that stays the same over time. It is a cytokine that is found in the blood and is generally thought to be a sign of systemic inflammation [26]. It's in plasma, and the amount in plasma goes up when there is an accident, an infection, or inflammation [27]. When CRP binds to the complement system, it raises the amount of dying cells, extracellular matrix components, cell receptors, growth factors, and the size of the infarct. In turn, this makes CVD worse [28].

Methodology

A comprehensive case-control study was conducted to investigate cardiovascular disease markers, comprising 50 participants diagnosed with cardiovascular conditions as the case group, and 25 healthy individuals as the control group. This study received approval from the Ethics Committee at the College of Medicine, Al-Nahrain University, and was carried out at Al-Nasiriyah Heart Hospital in Thi-Qar, Iraq, from March 1, 2022, to March 1, 2023. Detailed demographic and nutritional information for each participant was meticulously documented. Blood samples (5 ml each) were collected from all participants, with the samples allowed to clot at room temperature for 15 minutes. Following clotting, the samples were centrifuged at 3000 rpm for 15 minutes to separate the serum. The serum was then stored at -20 °C until further analysis. Quantification of cardiovascular biomarkers, including troponin, C-reactive protein (CRP), creatine kinase-MB (CK-MB), and B-type natriuretic peptide (BNP), was performed using the enzyme-linked immunosorbent assay (ELISA) technique. This methodological approach ensures accurate and reliable measurement of the biomarkers, facilitating a thorough comparison between the case and control groups.

Statistical analysis

Statistical analysis is often used to analyze quantitative data and provides methods for data description and simple inference for continuous and categorical data. The procedure involves the collection of data leading to a test of the relationship between two statistical data sets. All the information in this study is shown as the mean with a standard variation. The statistical studies were done with SPSS (version 26) and the dependent t-test (two-tailed) and the independent t-test (two-tailed) for variables with a normally distributed distribution. For variables with a non-normal distribution, the Mann-Whitney U test and the Wilcoxon test were used. $M < 0.05$ was seen as statistically significant.

Ethical approval

Before the samples were taken, all of the patients who were going to be part of this study were properly informed and gave their verbal permission. The Committee on Publication Ethics at the College of Medicine, Al-Nahrain University gave its approval to the study.

Results

Comparison of Demographic and Clinical Parameters Between Control and Patient Groups

The results of the study regarding the distribution of age and body mass index (BMI) between the control group and the patient group showed that there were no statistically significant differences between the two groups. The mean age of the control group members (n = 25) was 64.42 ± 7.66 years, while the mean age of the patient group members (n = 50) was 61.65 ± 7.76 years, with a probability (P) value greater than 0.05 indicating no significant statistical

difference. between the two groups in terms of age. Also, the mean body mass index (BMI) of the control group was 27.43 ± 4.83, while the mean BMI of the patient group was 26.86 ± 3.75, with a probability (*P*) value greater than 0.05, which also indicates that there is no significant statistical difference between the two groups of Where is the body mass index.

Table 1: Age and BMI Distribution in Control Versus Patient Groups

Parameters	Control group (n=25) Mean±SD	Patients group (n=50) Mean±SD	*P*. value
Age	64.42 ± 7.66	61.65 ± 7.76	>0.05^{NS}
BMI	27.43 ± 4.83	26.86 ± 3.75	>0.05^{NS}

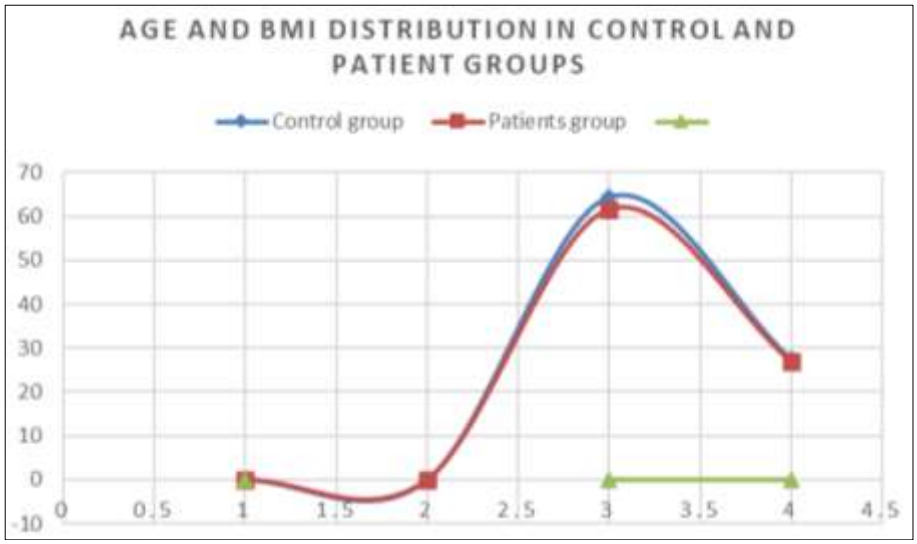

Fig 1: Comparison of age and BMI Between Control and Patient Groups

Comparative analysis of cardiac biomarkers in control and patient groups

The study results regarding the levels of CRP, troponin, BNP, and CK-MB between healthy individuals and heart patients showed significant statistical differences between the two groups. It was 2.21 ± 1.53 for the control group (n = 25) and 11.18 ± 4.45 for the patient group (n = 50). The (*P*) value was less than 0.001, which means there was a significant difference between the two groups. On average, the amount of troponin in the control group was 0.065 ± 0.028, but it was 7.64 ± 4.57 in the patient group, with a *P* value of less than 0.001, which means there was a significant difference. With (*P*) of less than 0.001, there was a significant statistical difference between the two groups. The average BNP level in the control group was 206.11 ± 43.50, while it was 776.82 ± 453.63 in the patient group. (*P*) value of less than 0.01 showed that there was a significant difference between the two groups. The average CK-MB level in the control group was 2.71 ± 1.11, while it was 4.33 ± 2.18 in the patient group. The levels of these biochemical markers are significantly higher in heart patients compared to healthy people, as these data show.

Table 2: Levels of CRP, Troponin, BNP, and CK-MB in Healthy Individuals Versus Heart Disease Patients

Parameters	Control group (n=25) Mean±SD	Patients group (n=50) Mean±SD	*P*. value
CRP	2.21 ± 1.53	11.18 ± 4.45	<0.001
Troponin	0.065 ± 0.028	7.64 ± 4.57	<0.001
BNP	206.11 ± 43.50	776.82 ± 453.63	<0.001
CK-MB	2.71 ± 1.11	4.33 ± 2.18	<0.01

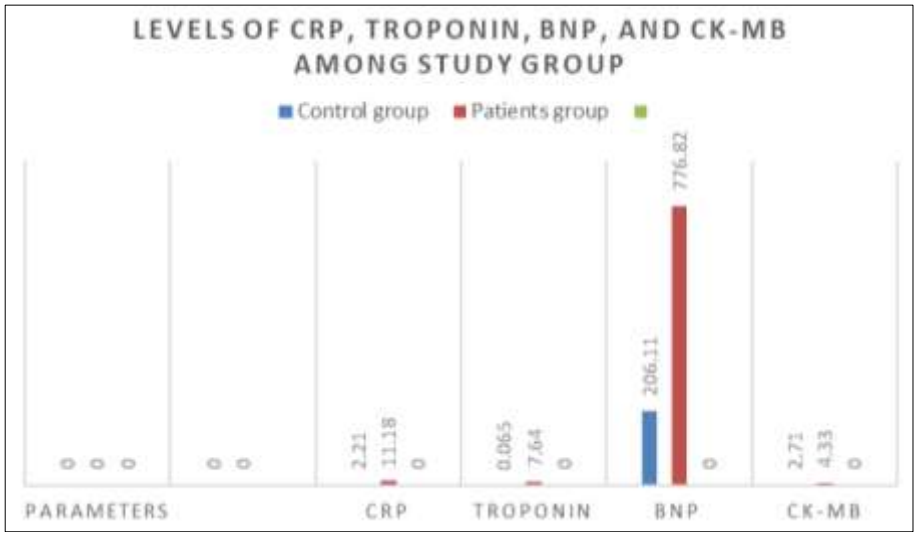

Fig 2: Comparative analysis of cardiac biomarkers in the study group

Correlation analysis between age and cardiac biomarkers in patient groups

The results of Pearson's correlation coefficient analysis and statistical significance levels of BNP, CRP, troponin, and CK-MB indices with age showed significant correlations. The Pearson correlation coefficient between age and BNP (r = 0.607) was statistically significant at the (*P* = 0.010) level, indicating a positive and strong association between age and BNP. Also, there was a positive correlation between age and CK-MB (r = 0.550) at a significance level (P = 0.012). However, there was no statistically significant correlation between age and CRP (r = 0.374, *P* = 0.105) or age and troponin (r = 0.262, *P* = 0.465). As for the relationships between the indicators themselves, BNP did not show a statistically significant association with CRP (r = -0.046, *P* = 0.862), troponin (r = -0.055, *P* = 0.906), or CK-MB (r = 0.138, *P* = 0.598). While CRP showed a positive and statistically significant correlation with CK-MB (r = 0.513, *P* = 0.021) and did not show a significant correlation with troponin (r = 0.306, *P* = 0.390). Troponin also did not show a statistically significant association with CK-MB (r = 0.537, *P* = 0.110). These findings highlight the potential complexities in the interactions between these different biochemical markers and demographic factors such as age in the study of heart disease.

Table 3: Pearson correlation coefficients and significance levels for BNP, CRP, Troponin, and CK-MB

Parameters		BNP	CRP	TROP	CK-MB
Age	Pearson Correlation	.607**	.374	.262	.550*
	Sig. (2-tailed)	.010	.105	.465	.012
BNP	Pearson Correlation	1	-.046	-.055	.138
	Sig. (2-tailed)		.862	.906	.598
CRP	Pearson Correlation	-.046	1	.306	.513*
	Sig. (2-tailed)	.862		.390	.021
Troponin	Pearson Correlation	-.055	.306	1	.537
	Sig. (2-tailed)	.906	.390		.110

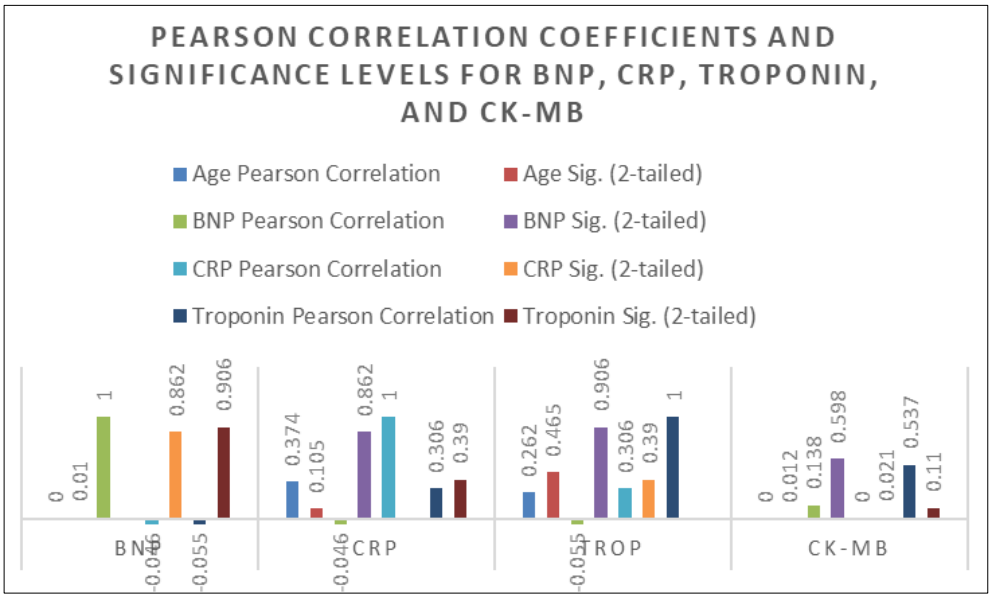

Fig 3: Correlation analysis between age and cardiac biomarkers in patient groups

Discussion

A lot of clinical studies have shown that hs-CRP can help identify CVD [29], and is also a biomarker and risk factor for CVD [30]. When people who have had an acute myocardial attack or acute coronary artery disease are checked for CRP levels, it may help find problems early on [31]. For the same reason, Hutchinson *et al.* [32] found in the first large-scale clinical studies that CRP levels go up directly with age. There may be a close connection between CRP and a higher chance of CVD. Ridker *et al.* [33], tracked the CRP levels of 27,939 patients for up to 8 years and discovered that higher levels of CRP were connected to a higher chance of CVD. A later study that looked at more than 6,000 patients showed that those with higher CRP levels had a higher chance of having an acute cardiovascular event [34]. These studies of large groups of people have shown that CRP may be able to predict CVD. As for the link between CRP and CVD, it has been proven that CRP can predict CVD. The link between CRP and CVD, on the other hand, has not yet been proven. Up to this point, the results of tests on animals and people have been controversial. The results of animal models need more study because animals and people are not the same. Over the years, CRP has been used as an acute-phase protein in clinical studies. Finding CRP has been shown to be useful in predicting CVD [35]. Several experts have said that CRP is a good way to tell if someone will get CVD [36]. But CRP has been connected to the work of smooth muscle cells, vascular cells, and monocytes/macrophages. It's also been found in plaques in arteries [37]. Previous research has shown that the liver creates CRP, which is then released into the bloodstream and sent to the inflamed tissue [38]. Still, no one knows for sure where CRP comes from. It would be very important to find out if CRP could help endothelial cells, monocytes/macrophages, and arterial smooth muscle cells move and multiply. This would begin the complement system and play a part in the development of CVD. Most experts, though, believe that more proof is needed to show that CRP activates endothelial cells and plays a part in the cause of atherosclerosis. With the information we have now, it is not clear what the cause-and-effect link is between CRP and CVD. To study the link between CRP and CVD for a long time, experts have used mice as models. However, there are some issues with this method [39]. To make better animal models that can better mimic the inflammatory reaction in humans, we need to figure out how CRP works on a local or global level. Right now, sources that are made

in a lab are used to figure out what part CRP plays in inflammation. This could be the most important thing to know about the current argument between CRP and CVD. According to the study, CRP that is released by the liver has a tough time getting into organs outside of the liver. If this is true, CRP could be made in organs outside of the liver and then sent back to the bloodstream [40]. Some people have become very interested in BNP over the last few years because it is a strong indicator of heart failure. It is also becoming a useful way to figure out how bad heart failure is because it is linked to the symptoms in a straight line. A lot of research has shown that BNP can be used on its own to raise the risk of heart disease and stroke. BNP is a strong indicator of whether a person with coronary heart disease will die within 6 months or need to be readmitted to the hospital. People with chronic heart failure (CHF) are more likely to be hospitalized and die suddenly if their BNP number is high. This means that BNP testing during CHF can help doctors figure out the amount of risk [41]. BNP levels below 100 pg/ml (negative) on the Triage BNP Test rule out heart failure. If the amount is more than 100 pg/ml, it means that the heart is failing. The lowest BNP level in our study was less than 100 ng/ml, and the highest level was 5000 ng/mL. This might be because a different way of measuring was used [42]. So hospitals should pick a way that is both accurate and easy, cheap, and able to fit the symptoms. We need to be more careful with the ELISA test. The most recent study shows that active BNP is not the only thing in blood. There is also BNP, BNP, and a lot of proBNP. Activated BNP isn't always detectable, even in very sick heart disease patients. This is because BNP1-32 breaks down very quickly and has a very small half-life. This is because the middle part of the peptide is glycosylated, which hides the antigen when we use an antibody that is made to attack this part of the peptide. In order for proBNP to not break down, the amino acids on its 8 binding sites must be glycosylated. This is especially true on the Thr71 site [43, 44]. Some people think that the damaged heart's real ability to survive failure can be seen in its ability to avoid making active BNP and change its form to proBNP [45]. A German study from the 1970s looked at how much creatine kinase and CK-MB were in the blood of 129 people with different types of heart failure. People with inflammatory heart disease made up most of the 19 people who had a high amount of CK-MB. They couldn't find a link between the amount of CK-MB in the blood and how bad the heart failure was [46]. In 162 people from Turkey, 104 had symptoms or signs of HF22 and 58 did not. The study looked at how CK-MB and cardiac troponin I were linked to the severity of HF. People with symptoms and NYHA classes III-IV had much higher mean values of CK-MB and cardiac troponin I than people with no symptoms and NYHA classes I-II. Another good thing about this study is that it had more patients (1,785) than the other ones that looked at the link between CK-MB and heart failure. Like other research, ours showed that HHF had a weak link to how well a person with SCHD would do in the future (HR 1.68, 95% CI 0.96 to 2.95, $p = 0.07$) [47]. A small prospective study from India looked at how cardiac biomarkers (like B-type natriuretic peptide, Tn-I, TNF-α, and CK-MB) were related to the result for 60 people with Framingham-classified heart failure [48]. B-type natriuretic peptide was a very good indicator, but CK-MB didn't change anything for this group of people. The results support what we found in our study, NT-proBNP and H-FABP were good indicators of HHF in SCHD patients, but hsCK-MB was not. At first, things like sex, diabetes, and high blood pressure were different between people with high and low hsCK-MB. Propensity score matching was used to cut down on the bias. The answer was the same whether the studies were done with or without adding the propensity score. It showed that hsCK-MB can be used to make predictions [49].

Conclusion

The study results showed that levels of CRP, troponin, BNP, and CK-MB were significantly higher in patients with heart disease compared to healthy controls, suggesting that these biomarkers are sensitive indicators of heart disease. An increase in the levels of these indicators reflects inflammation and myocardial damage, which enhances their role in the diagnosis and prediction of heart disease. The results also showed a positive association between age and levels of BNP and CK-MB, suggesting that increasing age can increase the likelihood of elevation of these indicators. These results support the importance of monitoring these biomarkers in patients at risk for heart disease to provide appropriate medical intervention.

Conflict of Interest

Not available

Financial Support

Not available

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