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CORRELATION OF SERUM HOMOCYSTEINE, URIC ACID AND C-REACTIVE PROTEIN LEVEL IN PATIENTS WITH ACUTE MYOCARDIAL INFARCTION

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ABSTRACT

Introduction: The term "acute myocardial infarction" (AMI) describes the destruction of heart muscle tissue brought on by ischemia, or the lack of oxygen to the heart's tissue. **Aim:** To investigate the correlation between serum levels of homocysteine, uric acid, and C-reactive protein in patients diagnosed with acute myocardial infarction (AMI). **Methods:** A total of 60 patients with AMI were enrolled in this study. After recruitment, detailed history was recorded and physical examination of subjects was carried out. A serum sample, used to determine the homocysteine, uric acid concentrations and other general biochemical assays, was obtained with one anticoagulant-free 7.5 mL test tube. Other biochemical assays were performed and CRP (mg/L) was measured. Subjects were grouped according to Killip classification. **Results:** In present study, mean Homocysteine (umol/l) in Killip class I was 4.86±2.01, in class II was 5.97±2.30, in class III was 8.44±4.73 and in class IV was 13.47±6.12 ($p < 0.01$). Mean uric acid (mg/dl) in Killip class I was 2.13±1.81, in class II was 2.54±1.74, in class III was 3.65±1.11 and in class IV was 4.51±1.07 ($p < 0.01$). Mean C-Reactive Protein (mg/l) in Killip class I was 0.72±0.57, in class II was 1.61±0.88, in class III was 5.96±3.03 and in class IV was 8.75±4.84, (p value <0.01). A statistically significant correlation was found between Homocysteine & Uric acid level with Coefficient of correlation being 0.58 (p value <0.01) ; between Homocysteine & C-Reactive Protein level with Coefficient of correlation being 0.43 (p=0.002) ; between Uric acid & C-Reactive Protein level with Coefficient of correlation being 0.41 (p value=0.005). **Conclusion:**The study found a significant correlation between blood levels of C-Reactive Protein (CRP), Uric acid, and Homocysteine with Killip classification in patients with Acute Myocardial Infarction. As the Killip classification stages progressed, the levels of these biomarkers also increased. There was a positive and statistically significant correlation between Homocysteine and Uric acid levels, Homocysteine and CRP levels, as well as Uric acid and CRP levels. These findings suggest that since these biomarkers are involved in Myocardial Infarction, monitoring their serum levels together could be beneficial for evaluating and managing these patients.

Keywords:C-Reactive Protein (CRP), Uric acid, Homocysteine , Killip classification , Acute Myocardial Infarction.

INTRODUCTION

The term "acute myocardial infarction" (AMI) describes the destruction of heart muscle tissue brought on by ischemia, or the lack of oxygen to the heart's tissue. It happens when a thrombus forms and the atherosclerotic plaque ruptures. Inflammation and necrosis of the cardiac tissue result in poor oxygen distribution and irreparable damage to the heart muscle. It also loses its capacity to contract and conduct impulses [1]. The development of drug-eluting stent technology, antiplatelet medicines, and emergency medical systems has made reperfusion treatment faster and more effective in the modern era. Nonetheless, the morbidity and mortality rates for AMI survivors are significant [2]. Thus, it will be useful to identify poor prognostic markers associated with AMI patients so that more thorough patient observation and effective preventative management may be carried out.

Among other things, studies conducted in the past 20 years have identified the amino acid homocysteine (HCY) as a stand-alone CVD risk factor [3-5]. The methionine (MeT) cycle primarily synthesizes hcy, an amino acid that contains sulfur and is not supplied by diet [6]. McCully was the first to document a link between high homocysteine

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levels and vascular disease [7]. Hcy damages the function of vascular endothelial cells, which ultimately results in CVD [9]. Mild to severe hyperhomocysteinemia is highly correlated with heart failure, restenosis, obstructive cardiovascular disease, percutaneous coronary intervention (PCI)-related death, reinfarction, and restenosis [11], as well as with all causes of death in such individuals [12]. This suggests that there may be a relationship between the status of antioxidants and the detected concentrations of HCY [12]. As a result, the risk of arteriosclerotic coronary lesions resulting from elevated HCY levels is mostly unknown, particularly in AMI patients.

An observational study found that premature vascular illnesses claimed the lives of almost 50% of children with familial homocysteinemia, indicating that homocysteine is a causative risk factor for childhood CVDs [15]. Additionally, prior research has demonstrated that taking supplements of B vitamins, like folic acid, can lower Hcy levels and stop cardiovascular illnesses from developing [16–19]. Finding early modifiable risk factors for CVD in teenagers is crucial to stopping the disease's progression and occurrence in adulthood.

It's interesting to note that studies looking into the relationship between blood uric acid levels and cardiovascular risk have produced conflicting and ambiguous results, with little information available regarding UA levels in AMI patients before PCI [20]. Serum uric acid raises oxidative stress and microvascular disorders by disrupting endothelial function [21]. A SUA level that is ≥5.5 mg/dL is considered high [22, 23]. Human purine metabolism culminates in the production of UA, which is generated by the enzyme xanthine oxidase, a source of reactive oxygen species (ROS) in the cardiovascular (CV) system [24]. After that, the kidneys and the intestines remove the UA [25]. Excessive UA production or decreased renal clearance lead to hyperuricemia (HUA) [26]. Significant impacts are noted at the levels of enhanced xanthine oxidase activity and UA concentrations. These two may serve as indicators for heart ischemia. A few studies also demonstrate a link between elevated UA concentrations and a higher incidence of CVD [11, 27, 29]. Myocardial infarction may be a consequence of the tissue damage caused by these processes.

The underlying mechanism of the correlation between uric acid and Hcy may be as follows: Within the human body, the MeT cycle occurs when MeT is converted to S-adenosylhomocysteine (SAH), which can then be further converted into Hcy and adenosine. Additionally, adenosine may be converted into uric acid, whereas hcy can replenish methyl meT [32]. It was expected that the combined effects of hyperhomocysteinemia and hyperuricaemia would have a greater impact on vascular endothelium changes because the primary mechanism of action of both HCY and UA in CVD is assumed to be oxidative damage on the vascular endothelium, which results in changes to endothelial cell vasodilatory properties due to disruptions in nitric oxide (NO) bioavailability and scavenging [34].

Conversely, antioxidant capability decreased and oxidative stress indicators increased when serum UA levels were artificially lowered [36]. Uric acid accounts for over half of the antioxidant serum capacity. By increasing tissue blood flow and decreasing vascular tone, it enhances endothelial function and may have a preventive effect on disorders linked to the cardiovascular system [23]. Certain clinical diseases have been documented to exhibit decreased serum concentrations [37].

When tissue damage or infection occurs in an acute phase, the liver is the primary site of synthesis for C-reactive protein (CRP), which is then discharged into the bloodstream. Serum C-reactive protein (CRP) levels significantly rise in inflammatory processes of many etiologies, either in conjunction with or apart from cardiac etiology [38, 39]. CRP circulates in extremely low amounts in healthy people [39], and elevated blood CRP levels are indicative of a systemic inflammatory. In addition to serving as an inflammatory marker, CRP is thought to be the most potent predictor of myocardial infarction and stroke [40]. The elevation of CRP expression in blood vessel endothelial and smooth muscle cells has a role in the higher level of serum UA that leads to systemic inflammation. This promotes its enhanced production and elevated level in circulation [41]. In the intima of the early atherosclerotic lesion, CRP causes the production of proinflammatory cytokines and produces terminal complement complexes, both of which contribute to the instability of the plaque [42].

METHODS:

This study was conducted as Hospital based prospective observational study. The research spanned a total of 12 months, from September 2022 to August 2023, following approval from the institutional research and ethical

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committee. The study took place in the Department of General Medicine at Mahatma Gandhi Medical College & Hospital, Jaipur.

Ethical Clearance and Confidentiality

Ethical clearance was obtained from the Institutional Review Board for Ethical Clearance at Mahatma Gandhi Medical College & Hospital, Jaipur. Participants and their attendants were informed about the study's procedures and objectives. Written informed consent was obtained from all participants or their attendants, with forms provided in the language best understood by them. Confidentiality of patient information was strictly maintained throughout the study. No alterations to the standard treatment plan were made for study purposes, and there was no additional financial burden on participants due to the study.

Study Population

The study included all patients who were diagnosed as Acute Myocardial Infarction on the basis of WHO Myocardial Infarction criteria. and were admitted to the inpatient department (IPD) at Mahatma Gandhi Medical College & Hospital.

Inclusion Criteria

- Age more than 18 years of either gender.
- Willing to participate in the study.
- Patients diagnosed as having acute Myocardial Infarction.

Exclusion Criteria

- All patients who were not willing to give consent.
- Patients who were taking drugs, which can alter the levels of CRP, Uric acid, Homocysteine.
- Patient with Pacemaker, heart-valve replacement Surgery.

Sample Size

Systematic Random Selection of every 3rd patient admittedto the IPD that was diagnosed as having Acute Myocardial Infarctionduring the study period was included.

Study Procedure

After recruitment in the study, detailed history was recorded and physical examination of subjects was carried out. A serum sample, used to determine the homocysteine, uric acid concentrations and other general biochemical assays, was obtained with one anticoagulant-free 7.5 mL test tube. Other biochemical assays were performed and CRP (mg/L) was measured. Subjects were grouped according to Killip classification.

KILLIP CLASSIFICATION

The Killip classification is a system used to assess the severity of heart failure in patients experiencing acute myocardial infarctionto predict their risk of mortality. It categorizes patients into four classes based on physical examination findings:

- **Killip class I:** Patients show no clinical signs of heart failure.
- **Killip class II:** Patients have rales or crackles in the lungs, an S3 heart sound, and elevated jugular venous pressure.
- **Killip class III:** Patients present with acute pulmonary edema (fluid in the lungs).
- **Killip class IV:** Patients are in cardiogenic shock or severe hypotension (systolic blood pressure < 90 mmHg) with evidence of peripheral vasoconstriction (oliguria, cyanosis, or sweating).

The classification helps clinicians stratify the severity of heart failure in myocardial infarction patients, with higher classes indicating a greater risk of mortality within the first 30 days post-infarction.

Statistical Analysis

The study conducted statistical analysis using data tabulated in Excel under the guidance of a statistician. Means and standard deviations were calculated for each group (SPSS 22.00 for windows; SPSS inc, Chicago, USA). Statistical comparisons were performed using one-way ANOVA, with a significance level set at $p < 0.05$.

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Formulas applied included:

1. **Mean:** Calculated as the sum of all values divided by the number of values ($\bar{x} = \Sigma xi / n$).
2. **Standard deviation (SD):** Used to measure the dispersion of data points around the mean (σ or s).
3. **ANOVA test:** Analyzed whether means of multiple groups differed significantly. This involved calculating:
    - **Sum of squares between groups:** Deviations of individual group means from the overall mean, squared and summed.
    - **Sum of squares within groups:** Deviations of individual data points from their group mean, squared and summed.
    - **F-ratio:** Ratio of sum of squares between groups to sum of squares within groups, determining if differences between groups are significant.
    - **Degrees of freedom:** Calculated as one less than the number of groups for sum of squares between groups, and total observations minus number of groups for sum of squares within groups.

This statistical approach helped analyze and interpret the correlation between serum levels of homocysteine, uric acid, and C-reactive protein in patients diagnosed with acute myocardial infarction (AMI).

Results

•**Gender Distribution**: There was predominance of males (n=39, 65%) and remaining 21 were females (35%).

•**Age Distribution**: Maximum subjects diagnosed with myocardial infarction were within 51-60 years of age (n=23, 38.33%), followed by 19 (31.67%) patients aged 41-50 years of age, 9 (15%) aged >60 years, 8 (13.33%) patients of age 31-40 years and only one (1.67%) subject was between 18-30 years of age group.

•**Risk Factors**: Dyslipidemia was the most common risk factor observed in 44 (73.33%) of patients, followed by Hypertension which was noticed in 41 (68.33%) patients. Other risk factors included were habit of Smoking was present in 27 (45%) subjects, Alcoholism was found in 32 (53.33%) patients, and Diabetes was present in 29 (48.33%) subjects.

•**Symptoms**: Maximum subjects presented with chest pain (n=55, 91.67%) followed by Dyspnea (n=51, 85%), Pedal Edema (n=37,61.67%), Orthopnea (n=33, 55%), Oliguria (n=26, 43.33%) and Abdomen Distension (n=23, 38.33%)

•**Mean Values**: Mean BMI among subjects was 25.72±4.45, mean systolic blood pressure was 156.46±13.74 and mean diastolic blood pressure was 89.09±8.21 mm Hg.

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•**Types of Myocardial Infarction**: Maximum subjects had NSTEMI (n=22, 36.67%), followed by 21 (35%) with AWMI, 8 (13.33%) with IWMI, 5 (8.33%) with ASMI and 4 (6.67%) with LWMI.

•**Killip Classification**: Maximum subjects were classified as class II (n=22, 36.67%), 17 (28.33%) as class I, 13 (21.67%) as class III and 8 (13.33%) as class IV.

•**Homocysteine (umol/l) with Killip classification** :

Table 1: Comparison of Homocysteine (umol/l) according to Killip classification

Killip Class	**Mean Homocysteine (umol/l)**	**SD**
Class I	4.86	2.01
Class II	5.97	2.30
Class III	8.44	4.73
Class IV	13.47	6.12
p value	<0.01*	

*: statistically significant

Mean Homocysteine (umol/l) in Killip class I was 4.86±2.01, in class II was 5.97±2.30, in class III was 8.44±4.73 and in class IV was 13.47±6.12, showing a statistically significant correlation between two (p value <0.01).

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- **Uric acid (mg/dl) with Killip classification :**

Table 2: Comparison of uric acid (mg/dl) according to Killip classification

Killip Class	**Mean Uric Acid (mg/dl)**	**SD**
Class I	2.13	1.81
Class II	2.54	1.74
Class III	3.65	1.11
Class IV	4.51	1.07
p value	<0.01*	

*: statistically significant

In present study, mean uric acid (mg/dl) in Killip class I was 2.13±1.81, in class II was 2.54±1.74, in class III was 3.65±1.11 and in class IV was 4.51±1.07, showing a statistically significant correlation between two (p value <0.01).

- **CRP (mg/l) with Killip classification :**

Table 3: Comparison of CRP (mg/l) according to Killip classification

Killip Class	**Mean CRP (mg/l)**	**SD**
Class I	0.72	0.57
Class II	1.61	0.88
Class III	5.96	3.03
Class IV	8.75	4.84
p value	<0.01*	

*: statistically significant

In present study, mean CRP (mg/l) in Killip class I was 0.72±0.57, in class II was 1.61±0.88, in class III was 5.96±3.03 and in class IV was 8.75±4.84, showing a statistically significant correlation between two (p value <0.01).

- **Correlation between homocysteine (umol/l), uric acid (mg/dl) and CRP (mg/l)**:

Table 4: Correlation between homocysteine (umol/l), uric acid (mg/dl) and CRP (mg/l)

Variables	**r value**	**p value**
Homocysteine & Uric acid	0.58	<0.01*
Homocysteine & CRP	0.43	0.002*
Uric acid & CRP	0.41	0.005*

*: statistically significant

A statistically significant correlation was found between Homocysteine & Uric acid level with with Coefficient of correlation being 0.58 (p value <0.01), Homocysteine& CRP level with Coefficient of correlation being 0.43 (p value =0.002) and Uric acid& CRP level with Coefficient of correlation being 0.41 (p value =0.005).

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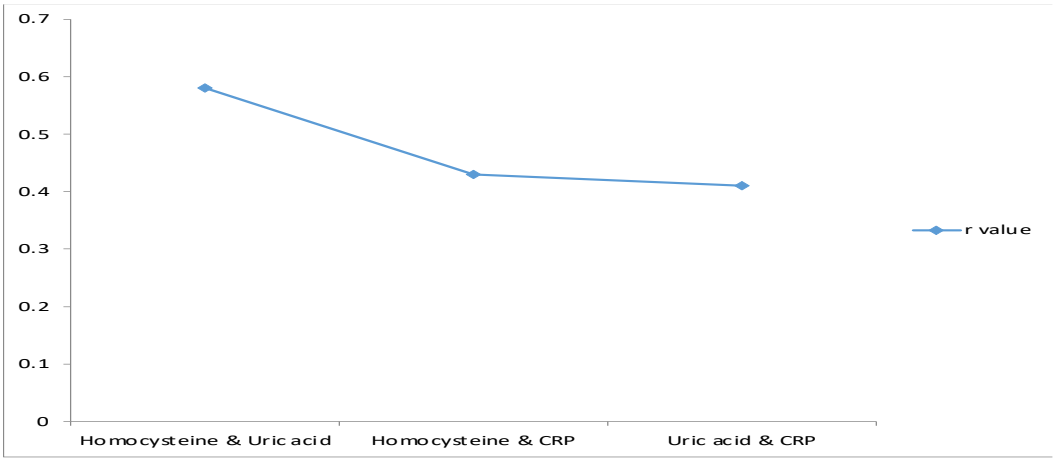
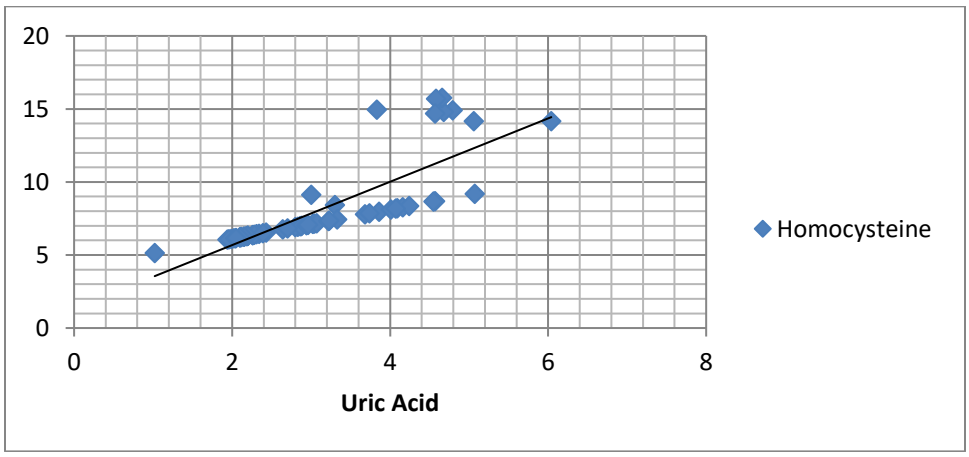


Graph 12: Correlation between homocysteine (umol/l), uric acid (mg/dl) and CRP (mg/l)



Graph 13: Correlation between homocysteine (umol/l) and uric acid (mg/dl)

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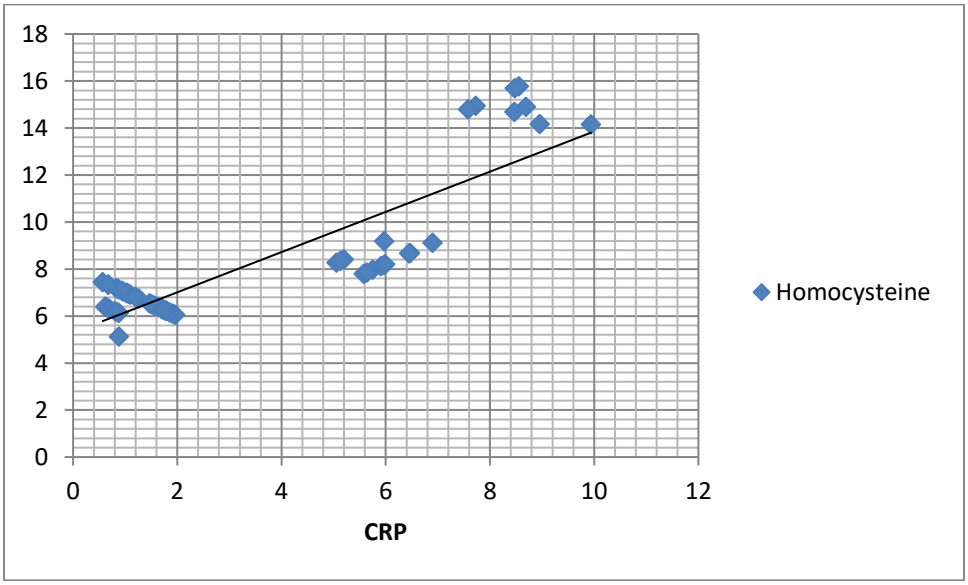
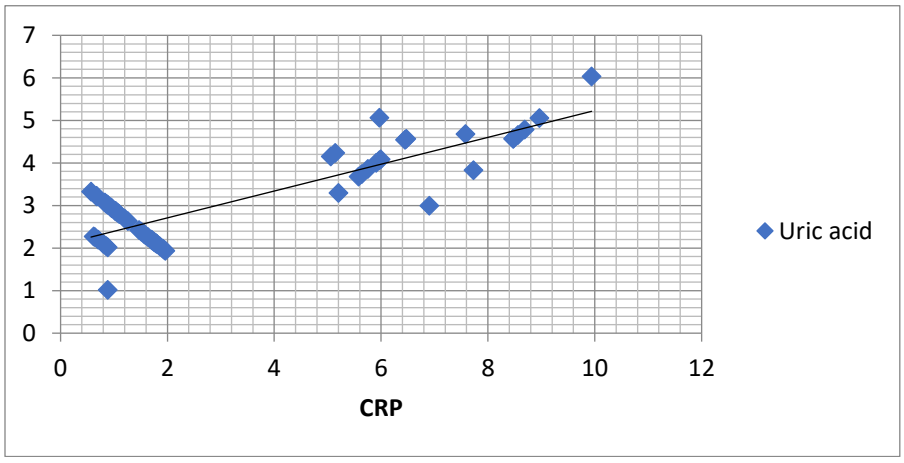


Graph 14: Correlation between Homocysteine (umol/l) and CRP (mg/l)



Graph 15: Correlation between Uric acid (mg/dl) and CRP (mg/l)

DISCUSSION

One of the cardiovascular consequences, acute myocardial infarction (AMI), is brought on by the rupture of atherosclerotic plaque and the formation of thrombus. The myocardium develops inflammation and necrosis, loses its ability to contract and conduct impulses, and ultimately experiences a reduction in the distribution of oxygen. Even though the individual effects of these medications are fairly well-known in AMI patients, further study is required to ascertain the level of interaction between Uric acid and Homocysteine and C-Reactive Protein, a crucial inflammatory measure. There is hardly much accessible data, and it often contradicts itself. Thus, the objective of the present investigation was to assess the homocysteine, uric acid, and C-Reactive Protein levels in patients with AMI before PCI was administered. The degree of association between these indicators in the blood of AMI patients with normal and increased C-Reactive Protein —which is believed to be a predictor of poorer cardiovascular outcomes—was more crucial to determine, though.

Gender distribution

In present study, there was predominance of males (n=39, 65%) and remaining 21 were females (35%). Similar results were observed by **Marković Boras M et al., (2018)**[43], found that of 85 patients included in the study comprised (61%) males and (24%) females.

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Age distribution

In present study, maximum subjects diagnosed with myocardial infarction were within 51-60 years of age (n=23, 38.33%), followed by 19 (31.67%) patients aged 41-50 years of age, 9 (15%) aged >60 years, 8 (13.33%) patients of age 31-40 years and only one (1.67%) subject was between 18-30 years of age group. **Marković-Boras M et al., (2021)**[44], found that median age in study subjects was 64.20±9.57 years, showing that AMI is common in elderly population, same as in our study. In study done by **Manjusha S et al., (2022)**[45], the mean age of occurrence of ACS was 58.32 years.

Risk factors

In present study, Dyslipidemia was the most common risk factor observed in 44 (73.33%) of patients, followed by Hypertension which was noticed in 41 (68.33%) patients. Other risk factors included were habit of Smoking was present in 27 (45%) subjects, Alcoholism was found in 32 (53.33%) patients, and Diabetes was present in 29 (48.33%) subjects. Similar results were observed by **Manjusha S et al., (2022)**[45], found that out of 50 cases with ACS, Dyslipidemia was the major risk factor (84%), similar to present study.

Symptoms

In present study, maximum subjects presented with Chest Pain (n=55, 91.67%)followed byDyspnea (n=51, 85%), Pedal Edema (n=37,61.67%), Orthopnea (n=33, 55%), Oliguria (n=26, 43.33%) and Abdomen Distension (n= 23, 38.33%). **Manjusha S et al., (2022)**[45], found that Dyspnea was found in 66% of the patients.

Type of acute myocardial infarction

In present study, maximum subjects had NSTEMI (n=22, 36.67%), followed by 21 (35%) with AWMI, 8 (13.33%) with IWMI, 5 (8.33%) with ASMI and 4 (6.67%) with LWMI. These results were concurrent with findings of **Manjusha S et al., (2022)**[45], found that 36% of the study subjects had NSTEMI, 36% had AWMI, followed by 14% having IWMI.

Killip classification

According to Killip classification, maximum subjects were classified as class II (n=22, 36.67%), 17 (28.33%) as class I, 13 (21.67%) as class III and 8 (13.33%) as class IV.

Homocysteine, uric acid and C-reactive protein

In present study, mean homocysteine level was 13.09±6.11, ranged between 5.13-15.77 umol/l, mean uric acid level was 4.1±1.6, ranged between 1.02-6.04 mg/dl and mean C-reactive protein level was 7.18±4.35, ranged between 0.57-9.94 mg/l.

This research reveals a positive correlation between the Homocysteine, Uric acid level and C-Reactive Protein levels with increasing of Killip's class in all patients tested, (p value <0.01). Similar findings were noted by **Marković Boras M et al., (2018)**[43], found that elevated level of both Homocysteine and Uric acid in AMI patients as well as a positive correlation between Homocysteine and Uric acid level was observed. **Manjusha S et al., (2022)**[45], also found higher serum C-Reactive Protein levels with increasing Killip's class (p value of 0.009).

Higher Killip classes have mean serum uric acid than lower classes, according to Bhattacharya PK et al. (2016) [46].They came to the conclusion that individuals with greater serum uric acid levels also had higher Killip classes, which indicate more serious disease. Furthermore, hospital stays were longer and in-hospital mortality was considerably higher among individuals with higher serum uric acid levels.

Patients with acute coronary syndrome showed a statistically significant higher level of blood uric acid concentration on the day of admission, according to Thakur CP et al.'s (2018) [47], analysis. Serum uric acid levels higher than 7 mg/dl and Killip's class (III, IV) were associated with higher death rates and serious adverse cardiac events. These findings align with our findings.

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Several studies, including Alam N et al., (2012) [5], Prajapati P, Panjwani SJ et al., (2016) [10], Marković Boras M et al., (2018) [43], have reported higher levels of Homocysteine in AMI compared to a group of healthy people. These findings are consistent with our research. Studies on the relationship between hyperhomocysteinemia and coronary artery disease, however, are conflicting. While some suggest a link (22, 23), others find no evidence of one and attribute the linkage to the high homocysteine levels found in the healthy population (24). Inconsistent outcomes can also arise from disparate standards for enrolling and disqualifying patients in studies, variations in patient populations, analytical techniques, genetic heritage, and dietary practices (25). Homocysteine blood concentration is directly influenced by a number of factors, including genetic background, adequate consumption of vitamins B6, B12, and folic acid, and sustained renal function. All of these aspects should be taken into account when analyzing Homocysteine concentration. The findings of our study are in line with those of Cohen E. et al. (2015) [34], similarly discovered a positive correlation between serum levels of uric acid and homocysteine. Other researchers, such as Verdoia M et al. (2015) [25], and Fu Z et al. (2015) [12], have obtained comparable results, which explains the link between Homocysteine and UA. Consequently, a rise in Homocysteine concentration causes an increase in Uric acid concentration.

A statistically significant connection was discovered in the current investigation between the levels of homocysteine and uric acid (p value <0.01), homocysteine and C-Reactive Protein (p value 0.005), and both. Killip's categorization and C-Reactive Protein level likewise shown a positive connection. C-Reactive Protein is helpful in the overall evaluation of cardiovascular risk since it is a measure of low-grade vascular inflammation (28). When a patient has angina pectoris or an AMI, it is thought to be a sign of a worsening cardiovascular prognosis. It also indicates the extent of cardiac injury (29). It was expected and proved that there was a link between the C-Reactive Protein level and Homocysteine and UA, taking these risk variables into account. Future research should take those issues into account, as there are other reasons besides atherosclerosis or AMI that might induce elevation of C-Reactive Protein levels.

Increased Homocysteine levels in patients with AMI are explained by recent studies that link them to more rapid development of thrombotic states [5], however the precise processes underlying these levels remain unclear. Due to its prothrombotic action, hyperhomocysteinemia is linked to platelet reactivity and is thought to be the cause of the decrease of carotid intima media (33) as well as the reported elevated level in AMI patients.. As a result, aspirin therapy may center on it (34). Homocysteine is linked to a number of health problems, including elevated arterial stiffness (35), reduced methylation potential, endothelial dysfunction, smooth muscle cell proliferation in blood arteries, oxidative stress, activation of NF-κB, inflammation, and suppression of nitric oxide generation in it. The finding that the combined effects of hyperhomocysteinemia and hyperuricemia had a greater effect on the previously described epithelial changes (26), further supports the synergistic impact of Homocysteine and Uric acid in CVD.

Elevated Uric acid levels stimulate the production of free radicals and an oxidative stress state, which in turn causes cardiomyocytes to undergo apoptosis and facilitates cardiac remodeling [27]. The result of all these alterations is a vicious cycle whereby the heart's functionality keeps declining (38).

From the earliest phases of atherosclerotic alterations to the final outcome, acute myocardial infarction, inflammation is a major factor in all of these processes. The study found that when Killip's categorization grade climbed, so did the levels of both inflammatory markers, C-Reactive Protein. According to Ekpenyong C. and Akpan E. (2014) [35], a high level of C-Reactive Protein is thought to be a reliable indicator of AMI. Profound systemic inflammatory markers in cardiovascular disease (CVD), C-Reactive Protein is also employed as a possible predictor of detrimental cardiovascular events (17, 18).

CONCLUSION

Our study has demonstrated a statistically significant correlation between blood levels of C-Reactive Protein ,Uric acid and Homocysteine and Killip classification in Acute Myocardial Infarction patients and their level increases as Killip’s classification stages progress . The Coefficient of correlation between Homocysteine & Uric acid level , Homocysteine & C-Reactive Protein level , Uric acid & C-Reactive Protein level was positive and statistically significant .This suggest that since these parameters are implicated in the Myocardial Infarction, their serum levels

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should be analyzed and evaluated together in these patients. Given the possible connection between them, more studies with a larger patient population need to be conducted.

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