Red Cell Distribution Width Value For Assessment Of The Severity Of Acute Coronary Syndrome And Its Correlation With Serum Indices- A Case Control Study

by

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ABSTRACT

BACKGROUND:

Acute coronary syndrome (ACS) is the syndrome including unstable angina pectoris and acute myocardial infarction syndrome, and is a common acute disease of cardiovascular system. ACS is with rapid development and poor prognosis, and can lead to different degrees of heart function damage, and effective auxiliary examination indexes are needed to early diagnose disease and predict prognosis. Red cell distribution width (RDW) is the index used to measure red blood cell volume variation and dispersion degree. In recent years, studies have confirmed that RDW has predicting effect on the risk of cardiovascular events and prognosis, and the risk of coronary disease is larger in population with higher RDW.

Objectives of the study:

Red cell distribution width (RDW) value for the assessment of the severity of acute coronary syndrome(ACS) and its correlation with serum indices.

Methodology:

Hospital based a case control study, a total of 90 cases of patients diagnosed with acute coronary syndrome and 90 cases of healthy individuals receiving physical examination were selected for study, and their serum was collected to detect RDW levels as well as the levels of cardiac biomarkers in the serum.

Results:

In our study, 90 cases of acute coronary syndrome had greater values of RDW (mean16.29%)

as compared to 90 age and gender matched controls mean 11.50%) with p-value of <0.001. It was also noted that, RDW values of patients of STEMI was greater than patients of NSTEMI and Unstable Angina

Conclusion:

RDW can assess the severity of acute coronary syndrome and is associated with degree of inflammatory response, myocardial ischemia and endothelial protection.

KEYWORDS: acute coronary syndrome, Red cell distribution width, RDW, STEMI, Myocardial infarction, endothelial protection

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LIST OF ABBREVATIONS USED

1	ACS	Acute coronary syndrome
2	RDW	Red cell distribution width
3	STEMI	ST elevation myocardial infarction
4	NSTEMI	Non-ST elevation myocardial infarction
5	UA	Unstable angina
6	PAD	Peripheral artery disease
7	COPD	Chronic obstructive pulmonary disease
8	LDL	Low density lipoprotein
9	HDL	High density lipoprotein
10	ECG	Electrocardiography
1	LV	Left ventricle
12	WHO	World health organization
13	IRI	Ischemia/reperfusion injury
14	cTN	Cardiac troponin
15	CK-MB	Creatine kinase (muscle/ brain)
16	MI	Myocardial infarction
17	TIMI	Thrombolysis in myocardial infarction score
18	BMI	Body mass index
19	LVEF	Left ventricular ejection fraction
20	RWMA	Regional wall motion abnormality
21	HB	Hemoglobin

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INTRODUCTION

INTRODUCTION

Acute Coronary Syndrome is the most common form of heart disease world-wide and the single most important cause of premature death. The disease of the coronary arteries is almost always as a resultant of atheroma formation and its associated complications. Atherosclerosis is an advancing inflammatory disorder of the arterial wall which is characterized by formation of atheroma, leading to occlusion of the vessel. It can affect any artery in the body and it begins in early life. One of the precipitating factor for the progression of atherosclerosis is presence of inflammation. Atherosclerosis begins with deposition of focal lipid rich deposits of atheroma, that remain clinically dormant until they enlarge and impair tissue perfusion. A vulnerable atherosclerotic plaque is characterized by a lipid rich core, a thin fibro-cellular cap and increased inflammatory cells that release specific enzymes to degrade the matrix proteins. As the vulnerable plaque ruptures, it consecutively leads to thrombus formation and occlusion of the affected coronary vessel, causing ischemia and necrosis of the subtended myocardium. These events that occur in the coronary arteries are termed as Acute Coronary Syndrome. [1]

Acute Coronary Syndrome(ACS) includes acute myocardial infarction (STEMI and NSTEMI) and unstable angina pectoris (UAP). ST-Elevation Myocardial Infarction (STEMI) and Non-ST elevation Myocardial Infarction (NSTEMI) are the components of Acute Myocardial infarction. [2]

Red blood cell distribution width (RDW) is a routinely measured parameter by modern Hematology analyzers. RDW is defined as the quotient of standard deviation of red blood cell volume and is expressed as a percentage according to the following formula: RDW= (standard deviation of red blood cell volume / mean cell volume) x 100. Red blood cell distribution width is a measure of degree of anisocytosis that is it is a measure of degree of variations in red blood cell volume. [3] RDW is a commonly used parameter to assess the degree and type of anemia. Recent studies show that RDW can also be used

as a prognostic marker for patients with heart failure. [4] Subsequent studies have confirmed the significance of RDW as a predictor of mortality in patients of various diseases including peripheral artery disease (PAD) [5], Chronic Obstructive Pulmonary Disease(COPD) [6], and end-stage renal failure. [7]

Inflammation plays a significant role in development of acute coronary syndrome and has a pathological link causing increased values of RDW. Under the conditions of enhanced inflammatory states, red blood cells undergo rapid destruction, slow maturation thus leading increased presence of immature and/or destructed red blood cells in the circulation and causing RDW levels to increase. [8] The advantage of using RDW is that, its assessment is easy, inexpensive, rapid and does not Require specialized skill sets or instrumentation. Another important advantage emerges from fact that its value is automatically generated by the modern hematological analyzers, and is hence measureable in virtually all the clinical laboratories performing routine or urgent testing.

In our research we have tried to establish a correlation between the RDW values of patients of acute coronary syndrome and cardiac biomarkers in assessing the severity of ACS as compared to normal healthy individuals.

AIMS AND OBJECTIVE

AIMS AND OBJECTIVES

1. To study the red blood cell distribution width (RDW) values for the assessment of the severity of acute coronary syndrome and its correlation with serum indices.
2. To compare the RDW values in patients of acute coronary syndrome with age and gender matched healthy controls.

REVIEW OF LITERATURE

INFLAMMATION AND ATHEROSCLEROSIS:

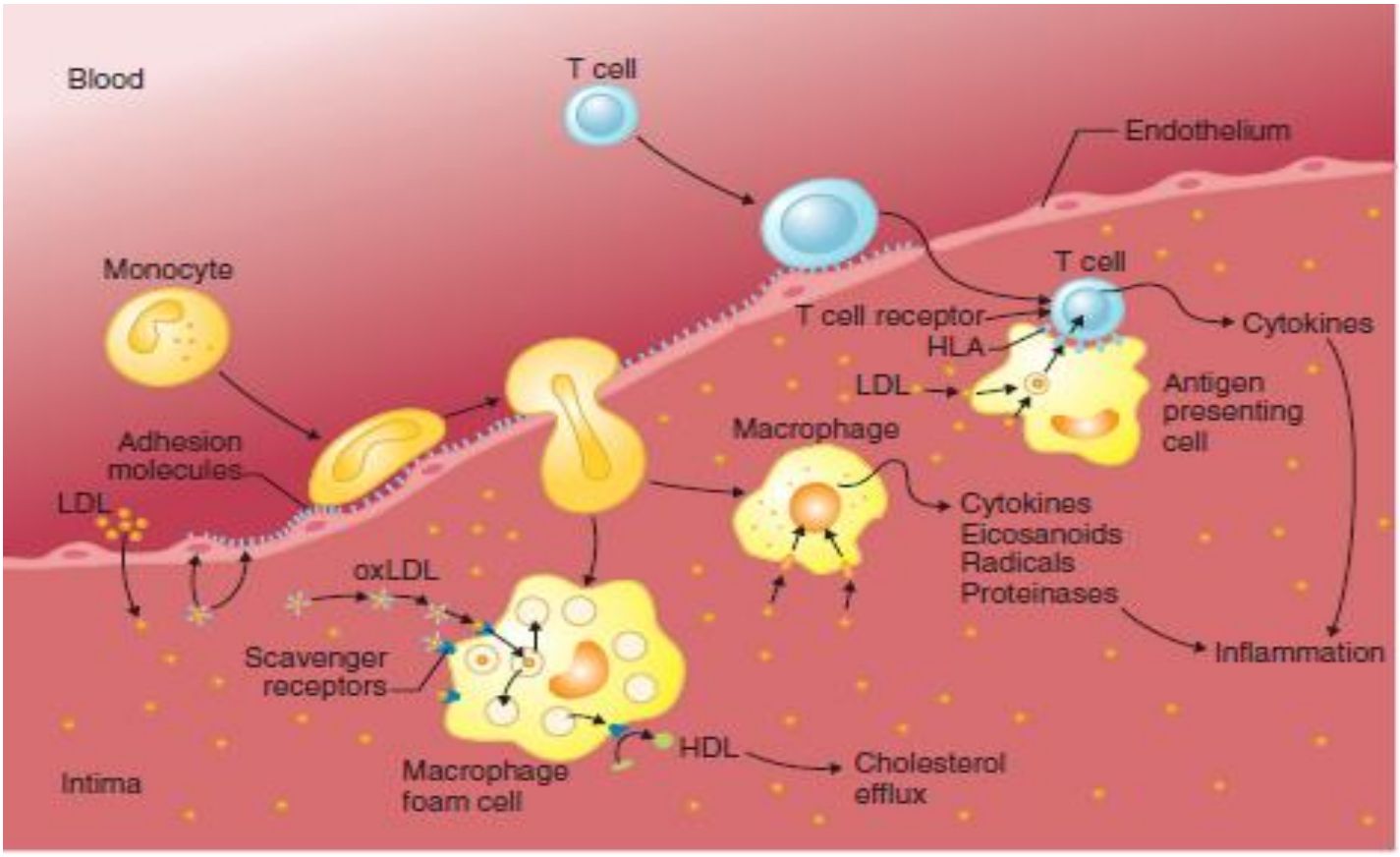
Atherosclerosis is defined as a chronic inflammatory response to accumulation of lipid in the wall of arteries and is characterized by clinically intimal plaques that develop in arteries. Atherosclerosis is the leading reason for most of the myocardial infarction, ischemic strokes and peripheral arterial disease, dementia and chronic heart failure. The major risk factors that facilitate the progression of atherosclerosis are hyperlipidemia, Obesity, smoking, type 2 diabetes mellitus, hypertension, high plasma levels of lipoprotein, psychosocial stress, sleep disturbances, elevated levels of serum homocysteine, elevated C-reactive protein and family history of coronary artery disease.

Inflammation plays a significant role at all the stages of development of atherosclerosis. The pathogenesis of atherosclerosis begins with interaction of endothelial cells and circulating leukocytes, resulting in T cell and macrophage recruitment and activation. As a consequence of this, smooth muscle cell accumulation and proliferation takes place, varying amounts of matrix production overlying an atheromatous lipid core, cholesterol, calcifications and necrotic debris; this constitutes an atheromatous plaque. Plaques vary in size and composition, most plaques remain asymptomatic, some become occlusive, and a few, become susceptible to rupture and lead to atherothrombotic events such as lethal cardiac arrest or incapacitating stroke.

The phenomenon of atherosclerosis commences when LDL accumulate in the vascular intima and get trapped in the wall of the artery. The trapped LDL particles are now attacked on by myeloperoxidase and NADPH oxidases. This leads to non-enzymatic oxidation of LDL, which further activates the macrophages and endothelial cells. This activation lead to T cell recruitment to the intimal layer of the arteries. The macrophages are known take up oxidized LDL and through the scavenger receptors, begin to gather cholesterol that eventually get converted to foam cells. The T cells identify the antigens presented by the macrophages (mostly LDL), and thus the accumulation of lipid in the intimal layer of arteries, triggers the chronic inflammatory process. The lipid rich plaques often have a hostile effect on the functioning of the

endothelium, thus leading to exaggerated retention of lipid particles into the endothelium and there by inhibiting the clearance.

As mentioned earlier most of the plaques remain stable, but a disruption of a partially occlusive plaques leads to thrombus formation and hemorrhage in to the core of plaques. This expands the plaque volume and thereby causing acute occlusion of the lumen of the arteries. [9]



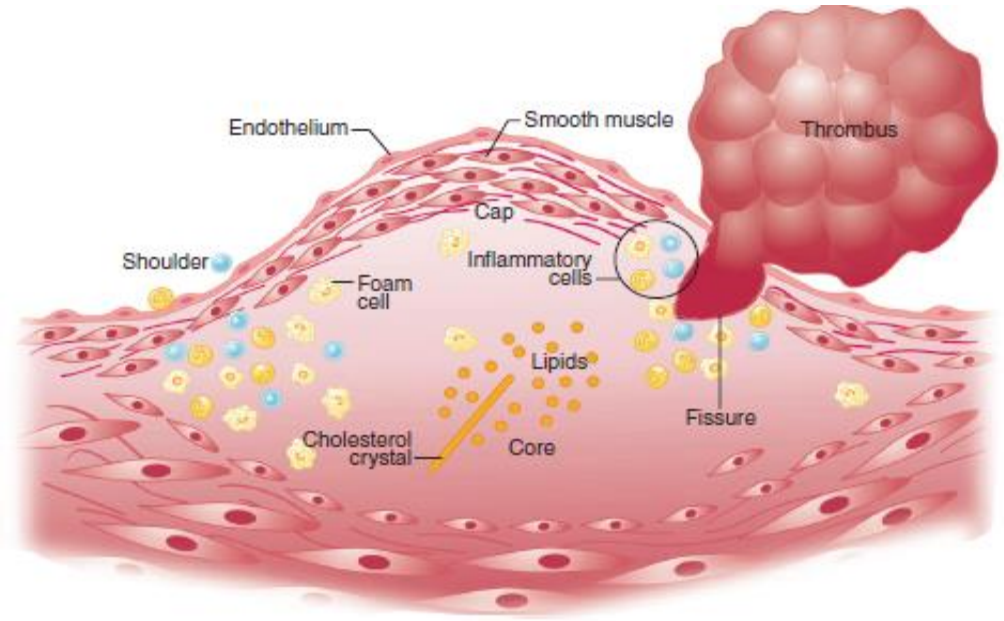
GROWTH AND PROGRESSION OF ATHEROSCLEROSIS:

The lesions of atherosclerosis gradually expand because of gathering of cholesterol, dissemination, activation and proliferation of inflammatory cells; further the core of the plaque grows due to the deposition of cellular debris and lipids. The collagen cap stabilizes the plaque mechanically but narrows the arterial lumen and the arteries undergo remodeling thus causing paradoxical vasoconstriction.

PLAQUE ACTIVATION, INFARCTION:

An atherosclerotic plaque usually remains stable and does not cause any clinical manifestations for days to years. However, if the surface of the plaque undergoes damage due to fissuring or plaque rupture, surface erosion can lead to sudden cardiac death. These events lead to formation of atherothrombosis. These atherothrombi rapidly expand and fill the lumen of the arteries leading to ischemia and infarction.

Thrombosis-prone atherosclerotic plaques, also known as high-risk or vulnerable plaques, are the main cause of death and severe disability worldwide. Although causal risk factors are known and constitute important therapeutic targets, their usefulness in risk assessment and finding people at the risk for an atherosclerotic event is limited. Most of the heart attacks and strokes occur in people who are not identified as being at particular high risk by conventional risk factor scoring. Atherothrombotic events are however, always preceded by a long pre-clinical phase in which sub-clinical atherosclerosis evolves and can be detected by non-invasive techniques and thereby offering unique opportunities for timely and individualized preventive care. [10]



DEFINITIONS OF ACUTE CORONARY SYNDROMES:

Coronary artery disease forms about 30% of all worldwide deaths. The global rise in problem of cardiovascular disease is because of the rising incidence of low-middle-income countries. Concordant changes have befallen over the past decade in the epidemiology of acute coronary syndromes as a result of changing demographics and updated definitions of Myocardial Infarction. [11]

The term Acute Coronary Syndrome (ACS) encompasses a spectrum of ST-elevation Myocardial Infarction (STEMI), Non-ST elevation Myocardial Infarction (NSETMI), and Unstable Angina (UA).

Unstable Angina:

"The patients of unstable angina (UA) present with chest pain secondary to abrupt reduction in the myocardial perfusion as a result if non-occlusive coronary thrombosis. In this episode, however the non-occlusive thrombus that advanced on a disordered atherosclerotic plaque does not result in biochemical evidence of myocardial necrosis." [12]

As a result of dearth of unbiased criteria used to define unstable angina, one must rely on most subjective evidences for the diagnosis of ACS. The major presentations of Unstable angina are as follows:

1. Chest pain or angina at rest or on minimal exertion that usually lasts for 20 minutes.

2. New onset chest pain
3. Crescendo angina defined as “previously diagnosed angina that has become noticeably more frequent, hastened by less severe degrees of exertion or more severe” [13,14]

Non ST Elevation Myocardial Infarction (NSTEMI):

“The diagnosis of Acute Myocardial infarction was defined by the World Health Organization (WHO) based on the following three criteria:

1. Presence of typical chest pain, retrosternal, lasting for more than 20 minutes
2. Typical ECG pattern including development of pathological Q waves
3. Rise and fall in serum markers of myonecrosis.

If the patient did not have ST segment Elevation or Q waves but has typical rise and gradual fall of serum troponin levels or a more rapid rise and fall of creatine kinase myocardial band (CPK-MB), the patient was diagnosed to have NSTEMI. [15,16] The patients of unstable angina and NSTEMI have the same pathophysiology.”

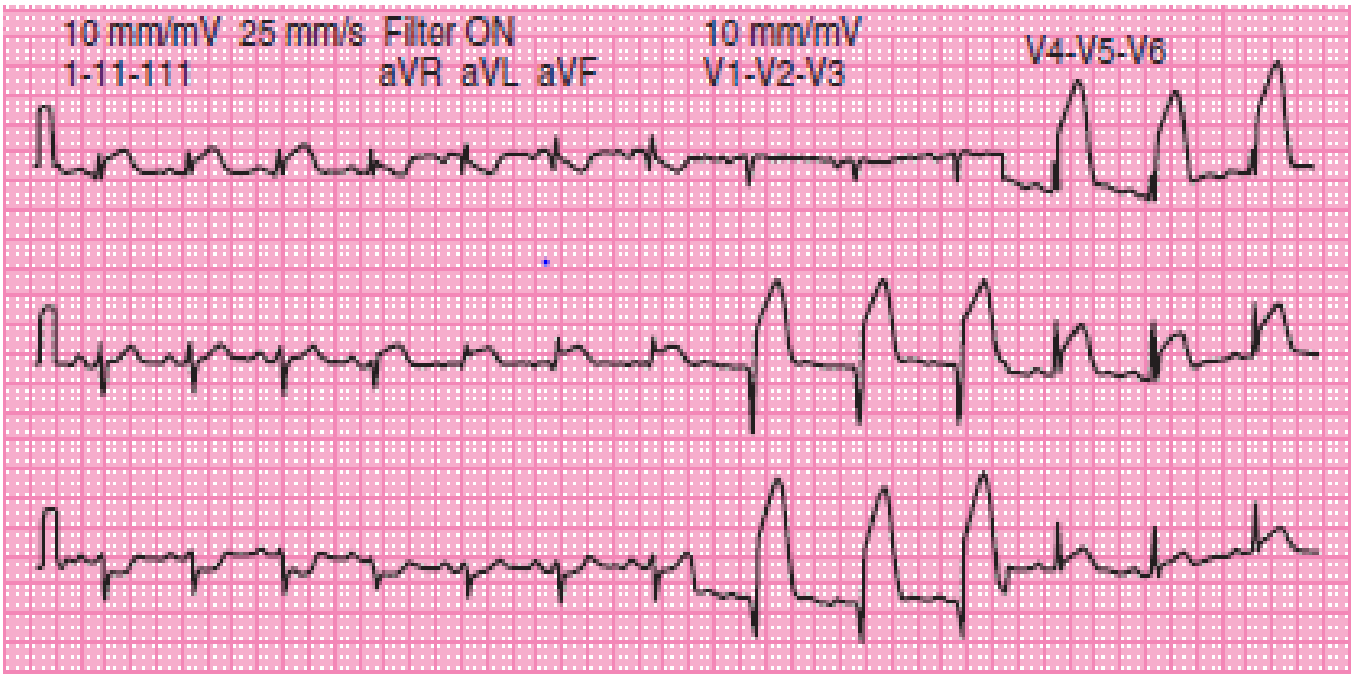
ST Segment Elevation Myocardial Infarction (STEMI):

ST- Segment Elevation Myocardial Infarction is the most lethal form of Acute Coronary Syndrome that occurs as a resultant of complete occlusion of the coronary blood flow, that manifests electrically as elevation of ST segment on ECG.

Pathological Q waves may progress because of full or near complete necrosis of the ventricular wall segment supplied by the artery. Early diagnosis of STEMI is of utmost importance because these patients require immediately thrombolysis or percutaneous coronary intervention.

In a suitable clinical setting, a pattern of ST segment elevation of 2 mm (0.2 mV) or more at the J point in V2 to V3 in men or 1.5 mm (0.15 mV) or more in women in the absence of left ventricular (LV) hypertrophy or 1 mm (0.1 mV) or more in two or more other contiguous

chest or limb leads suggests coronary occlusion causing marked myocardial ischemia. [17] In such patients, emergency reperfusion (primary angioplasty or fibrinolysis) should be performed unless it is contraindicated. Hyper acute T wave changes may suggest the diagnosis in the early phase of STEMI before the onset of ST elevation. A new or presumably new LBBB, which may obscure ST elevation analysis, may suggest STEMI equivalent in the appropriate clinical setting. ST depression in two or more precordial leads V1 to V4 may indicate transmural posterior injury due to occlusion of the left circumflex coronary artery; extending ECG analysis to leads V7 to V9 can help confirm this diagnosis.

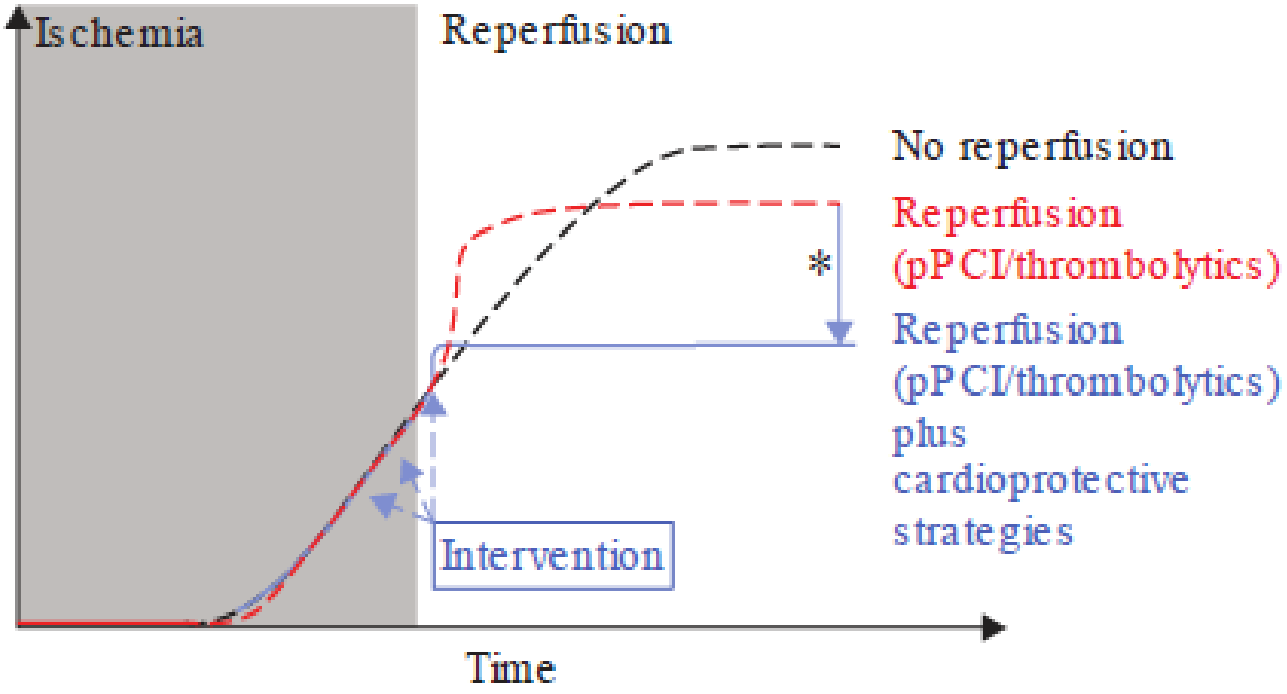


MOLECULAR AND CELLULR MECHANISMS OF MYOCARDIAL ISCHEMIA AND REPERFUSION INJURY:

The myocardium that is supplied by the occluded artery experiences severe ischemia. Prolonged duration of ischemia, (if there is no collateral circulation), results in irreversible damage to the myocardium, which leads to formation of fibrotic non-contracting tissue (myocardial scar). Depending on the size of the territory distal to the occlusion site, the global ventricular function can be significantly impaired, resulting

in post-infarction chronic heart failure.[18] Classical studies performed in large animal models demonstrated that blood flow restoration (reperfusion) was able to limit the progression of myocardial injury in a timely manner.[19] Reperfusion was shown not only to limit the progression of myocardial death but also to change the pattern of myocardial tissue healing. This concept was rapidly introduced into the clinics, and a long series of successful trials demonstrated that early reperfusion was able to reduce the extent of myocardial injury and, more importantly, to reduce mortality. Since then, timely reperfusion has become the standard treatment for patients suffering an acute myocardial infarction. Extensive preclinical and clinical studies have shown that reperfusion itself induces damage to the formerly ischemic myocardium. Atherosclerotic plaque rupture and thrombus results in sudden cessation of oxygen and nutrient supply distal to the occlusion site. The re-opening of the epicardial vessel by mechanical or pharmacologic means, in addition to the reduction in thrombus load by adjuvant antiplatelet/anticoagulant therapies, is only the primary step towards the salvaging the myocardium. During the reperfusion process (whether it is mechanical by primary angioplasty or pharmacologic by thrombolytics), thrombus material and other plaque debris can embolize, causing microvascular obstruction (MVO). “Circulating cells add to the injury caused to the myocardium, activated platelets and leukocytes in the bloodstream not only cause thrombus generation, but also can form plugins that can embolize distally into the microcirculation through resting blood flow across the lesion (a process independent from plaque debris microembolization). The microcirculation is an important factor in deciding the fate of the myocardium during ischemia/reperfusion. Once the epicardial vessel flow is reinstated, efficient tissue perfusion is dictated mainly by the microcirculation. Plaque debris and platelet/neutrophil aggregates cause mechanical obstruction of the microcirculation preventing efficient tissue perfusion despite the opening of the epicardial artery (which is known as the no-reflow phenomenon).” As a result of tissue edema following reperfusion results in external compression of the microcirculation, thus reducing the perfusion capacity of the capillary network. Finally, the microcirculation gets fragmented as a result of previous damage, which allows circulating cells to leak

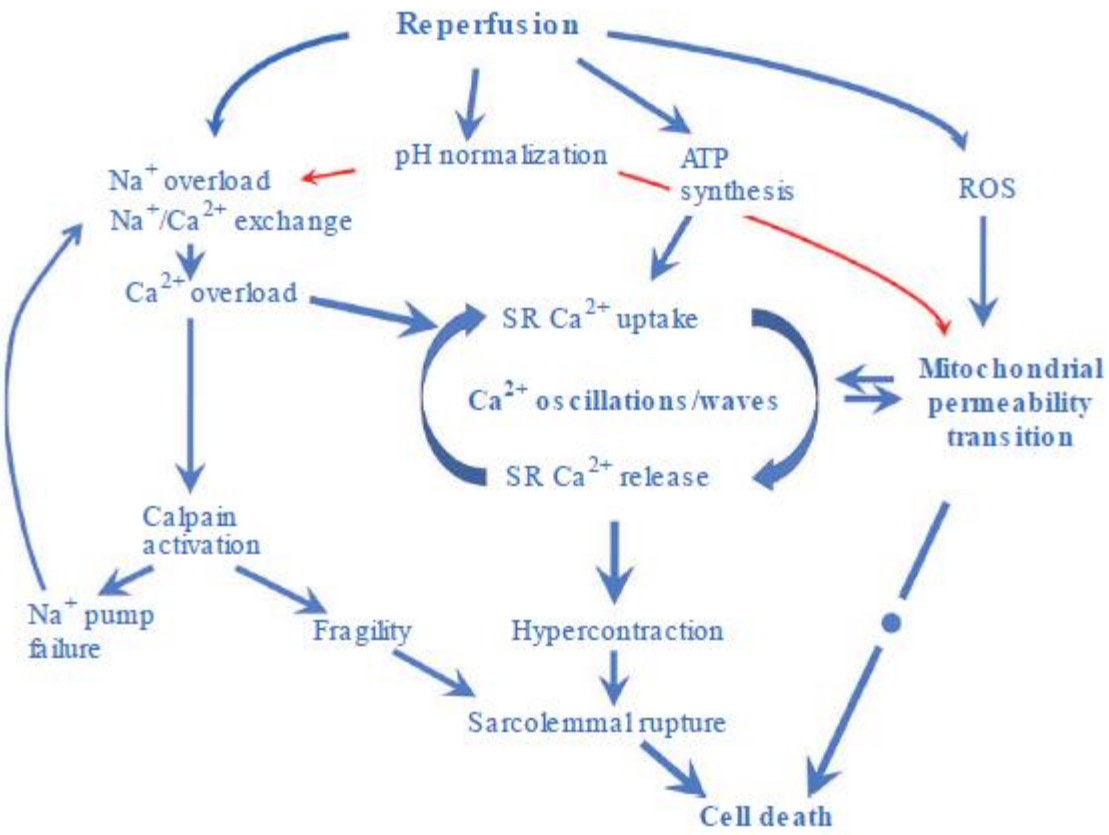
into the interstitial space. Hemorrhage is especially harmful because of the release of iron, adds to subsequent inflammatory reactions. “Cardiomyocytes that have survived the ischemic phase suffer during the reperfusion period as a result of several intracellular pathways triggered at reperfusion. After the acute phase of the ischemia/reperfusion insult has passed, the infiltration of myocardial tissue by inflammatory cells induces additional damage to the myocardium.” [20]



Cardiomyocyte death secondary to reperfusion injury is mainly dependent on mechanisms taking place within cardiomyocytes themselves. In fact, the most important aspects of Ischemia/ reperfusion injury (IRI) in the intact heart can be recapitulated in isolated cardiomyocytes submitted to transient hypoxia/ reoxygenation or to similar conditions. [21-23] However, inflammatory cells can cause cardiac myocyte cell death due to myocardial reperfusion. The mechanism of these interactions is complex and incompletely understood and may take place irrespective of impairment of microvascular flow. For example, platelet activation and adhesion increase cardiac myocyte death independently of aggregation and of any effects on myocardial flow. [24,25] It is widely admitted that a large fraction of cell death caused by lethal myocardial IRI occurs during the initial minutes of reperfusion, thus requiring early administration of cardio-protective

interventions in order to prevent it. Some studies have suggested the existence of additional delayed IRI during the first hours of reperfusion, but the importance of this phenomenon needs to be established. In this context, it is important to notice that non-cardiomyocyte cells have a better tolerance to ischemia than cardiomyocytes. This is particularly relevant in the case of endothelial cells, the metabolism of which is largely independent of mitochondrial respiration Although there have been controversies about the contribution of apoptosis to IRI, it is clear now that IRI causes cardiomyocyte death mainly through necrosis. It has been described that adult cardiomyocytes do not express executioner caspases 3 or 7 and that their selective genetic ablation does not modify infarct size or post-infarction remodeling in mice submitted to transient coronary occlusions. Recent studies have shown that necrosis may occur in different forms, ranging from sarcolemmal rupture resulting in massive calcium overload to programed forms of necrosis involving precise signal cascades, in particular necroptosis, a form of programmed necrotic cell death dependent on receptor-interacting protein kinase. Reperfused infarcts are mainly composed of contraction band necrosis, a pathologic pattern reflecting sarcolemmal disruption and extreme cell shortening. [26]

The long existing debate over the presence of lethal reperfusion injury was ended by the recognition of the ischemic preconditioning phenomenon when Jakob Vinten-Johansen reported that repeated coronary re-occlusion during early reperfusion caused reduction in infarct size.[27] With the clear concept that reperfusion is both obligatory to save myocardium from impending infarction and it also causes irreversible injury, a complex picture arises that both ischemia and reperfusion ultimately cause injury, but their individual influence to definitive injury depends on the span and severity of coronary blood flow reduction. Although ischemic injury escalates with the severity and the span of coronary blood flow reduction, there is a maximum of reperfusion injury in more moderate ischemic injury. The manifestations of reperfusion injury are micro-embolization, edema, microvascular obstruction and capillary hemorrhages. [28-31]



BIO-MARKERS OF CARDIAC-MYONECROSIS:

Serum biomarkers that indicate myocardial injury and/or necrosis are important components in the diagnosis of a patient with anticipated cardiac chest pain and are vital to distinguish between Unstable Angina and infarction. In an ideal setting, biomarkers should have been specific to cardiac muscle, that are released rapidly into the blood after onset of myocardial injury, and also reveal the degree of necrosis. Above all, it should be easy to use, quick to diagnose Unstable angina. [32] Whether or not the diagnosis of UA will persist as a distinct clinical entity with the ongoing evolution of high-sensitivity cTn assays has been questioned and remains controversial. From a prognostic point of view, “cTns exhibit a graded, dose dependent association with increasing cardiovascular risk. In addition, changes in cTn confer an

autonomous and stronger impact on subsequent risk than clinical symptoms, ECG signs, or other biomarkers."[33] In terms of treatment, randomized trials have shown the beneficial impact of managing patients with elevated levels of cTn in an aggressive fashion using potent antiplatelet, anticoagulant, and invasive approaches. These findings form the foundation for current guideline recommendations that support the routine measurement of cTn in diagnostic and therapeutic algorithms for ACS patients. Similar findings were also reported in an observational study evaluating the impact of implementing a sensitive troponin assay on the classification and management of ACS patients in clinical practice. [34] Given the benefits of cTn in assessing and formulating clinical decisions, the Universal Definition of MI considers this biomarker preferentially over CK-MB. The advantages to cTn testing nevertheless, as with any diagnostic test, gains in sensitivity occur at the expense of specificity. This paradigm also extends to measuring troponin and is particularly relevant given the iterative evolution of even more sensitive troponin assays. Various studies have shown that troponin elevations can be observed in other conditions such as heart failure, renal dysfunction, and pulmonary embolism. Troponin may even be detected in apparently healthy community-dwelling adults, as shown in the Dallas Heart Study. [35] Various investigators found the following clinical conditions independently associated with detectable levels of cardiac troponin: left ventricular hypertrophy, diabetes mellitus, chronic kidney disease, and heart failure. Newby et al [36] introduced a concrete model to describe the countless scenarios in which elevated levels of serum troponin might be detected. However, 'not all elevated troponin represents an MI and that not all myonecrosis reflects an ACS event, even when ischemic in etiology'. Hence, the diagnosis of MI requires not only elevated cardiac troponin level, but also a clinical context supporting an ischemic etiology. The underlying pathophysiology of elevations in serum troponin outside the ACS context remains unclear. Postulated mechanisms surround normal cellular turnover, which might be accelerated by age, exercise, or other factors, and increases in myocyte cellular permeability as a result of transient episodes of ischemia. [37,38]

Cardiac-derived TnI (cTnI) and TnT (cTnT), which are proteins of the sarcomere, are not usually

present in the blood with standard sensitivity assays and have amino acid sequences are diverse from their skeletal muscle isoforms. “The troponins mostly are first detectable 1 to 4 hours after the onset of acute MI, are maximally sensitive at 8 to 12 hours, peak at 10 to 24 hours, and persist for 5 to 14 days. Their long persistence has allowed them to replace other markers for the diagnosis of acute MI in patients presenting late (>1 to 2 days) after symptoms”. [39]

The sensitivity and specificity of cardiac-specific TnI and TnT make them the “gold standard” for diagnosis of myocardial necrosis. Nonetheless, because of the delay after the onset of symptoms, before markers become detectable or diagnostic across the spectrum of acute coronary syndromes, the decision to proceed with urgent reperfusion (primary angioplasty or fibrinolysis) in STEMI must be based on the patient’s clinical history and initial ECG.

In summary, cardiac troponins have emerged as the biochemical marker of choice in the evaluation of myonecrosis and diagnosis of MI. Their greater sensitivity and specificity for cardiac muscle damage and proven prognostic value have established their current clinical position. Gains in troponin assay sensitivity may continue to decrease the incidence of troponin-negative ACS or UA, while increasing the number of patients diagnosed with NSTEMI

RHEOLOGY OF BLOOD IN ACUTE MYOCARDIAL INFARCTION:

Acute myocardial infarction (ACS) is known to cause various abnormalities in the rheology of blood flow because of myocardial ischemia in terms of increase in blood viscosity and plasma proteins. [40] “The substantial increase in blood viscosities in patients with acute myocardial infarction were thus due to: 1) an initial increase in Hematocrit value, and 2) more sustained changes in plasma protein concentrations with resultant increases in plasma viscosity and the tendency of red cell aggregation. The increased blood viscosity might result in an increase of flow resistance in the microcirculation of acutely injured heart as well as in the remainder of the body.” [41]

RED CELL DISTRIBUTION WIDTH (RDW):

"Red Cell Distribution Width (RDW) is a routine use parameter by modern hematology analyzers. RDW is defined as the quotient of standard deviation of red blood cell volume and its mean volume and is expressed as a percentage according to the following formula:

RDW = (standard deviation of red blood cell volume/ mean cell volume) x 100"

RDW values reflect variation in red cell volume. More recently RDW is measured by analog computation technique using the new automated analyzers. [42] "The total number of erythrocytes counted are threshold circuit. This threshold begins at a level equivalent

classified by size by an automatic, continuously variable to 360 femtoliters and moves progressively lower until 20% of all the erythrocytes present have greater size than threshold. The cell size at which this occurs is the 20th percentile value (A). The threshold continues threshold downward until 80% of all erythrocytes have a size greater than the threshold. The cell size at which this occurs is recorded as the 80th percentile value (B), and the values are computed through the equation RDW= [(A- B) / (A + B)] X K (constant). The RDW thus represents the coefficient of variation of the red blood cell volume distribution and can be he considered as an index of heterogeneity, the equivalent of anisocytosis observed in a peripheral blood smear. with increasing reliability on electronic particle counters in clinical hematology laboratories, the RDW is a common feature of the automated complete blood cell count" [43,44]

RED CELL DISTRIBUTION WIDTH (RDW) IN CARDIOVASCULAR DISORDERS:

In recent years' various studies have identified RDW as an index for predicting cardiac mortality and systemic inflammation. [45] Increased values of RDW has been linked to adverse consequences in patients with myocardial infarction, heart failure and stable coronary artery disease(CAD) irrespective of hemoglobin levels. [46-48]

Interestingly, both inflammation and neuro-hormonal activation can alter bone marrow sensitivity to erythropoietin resulting in release of immature red cells into the circulation. This leads to presence of largely variable size of erythrocytes, which is quantified by RDW.

Ischemia along with sustained and persistent inflammatory reaction almost always accompanies cardiovascular disorders and has been associated with considerable abnormalities of erythropoietin production which then promotes the release of erythrocytes of different sizes from bone marrow. Increased oxidative stress in RBCs may result in deterioration in the mechanical properties of these cells and give rise to impairment in tissue perfusion which may further reflects on increased RDW levels.

Table 1: Important studies demonstrating the correlation between RDW and cardiovascular diseases:

AUTHOR	CONCLUSION
Uyarel H, Ergelen M et al [49]	"Higher admission RDW values in patient undergoing PCI for STEMI were associated with long term cardiovascular mortality"
Polat et al. [50]	"High RDW was an independent predictor of high GRACE score, and it is associated in hospital mortality in UAP/non-STEMI".
Halit Acet, Faruk Ertas et al. [51]	"RDW is an independent predictor of worse GRACE risk score in patients with STEMI"
Alejandro Rosas-cabral et al. [52]	"RDW as a prognostic factor of short term cardiovascular mortality in ACS patients"
Gianni turcato, Valentina Serafini et al. [53]	"RDW may be a valuable , easy and inexpensive parameter for stratifying the medium-term risk in patients with ACS".

In our study we have tried to correlate the RDW levels in patients of ACS with that of age and gender matched healthy controls. We also have tried to correlate RDW of patients with NSTEMI, STEMI and unstable angina; with serum cardiac biomarkers and 2D Echocardiography findings.

METHODOLOGY

METHOD OF COLLECTION OF DATA:

All the patients diagnosed with acute coronary syndrome and admitted to the BLDE's Shri B.M. Patil Hospital, Vijayapur will be recruited under the study after receiving informed consent for the study, detailed physical examination and serum samples will be collected.

INCLUSION CRITERIA:

All the patients diagnosed with Acute Coronary Syndrome as described by the criteria of American College of Cardiology and European Heart Association of Cardiology.

EXCLUSION CRITERIA:

1. Liver disease
2. Autoimmune diseases
3. Cancer Disorders
4. Hematological disorders
5. Severe valvular disease
6. Inflammatory Disease
7. Infectious diseases
8. History of bleeding diathesis.
9. Patients on the following medications will be excluded from the study: corticosteroids, cytotoxic drugs, thrombolytic therapy, and glycoprotein IIb/IIIa inhibitors.
10. Age less than 18 years
11. Patients who withdraw the consent for the further participation in the study.

TYPE OF STUDY – CASE- CONTROL STUDY

SAMPLE SIZE:

With Anticipated Mean Difference of Mean RDW between the two study groups as 3.5 and Anticipated SD as 6.4, the minimum sample size per group is 87 with 90% power and 5% level of significance.

By using the formula:

n= (Zα +Zβ)2 2 SD2/ MD2

Where Z= Z statistic at a level of significance

MD= Anticipated mean difference

SD= Anticipated Standard deviation

STUDY PERIOD: 15th November 2017 to 31st March 2019

STUDY SITE: Cardiac ICCU of Shri B. M. Patil Medical college hospital and Research Centre, Vijayapur.

Enrolment and investigations:

On admission, the patients of acute coronary syndrome fulfilling the inclusion criteria were assessed for their severity using TIMI score and KILLIP class. Variables at baseline for each patient were age, gender, reason for admission, anthropometry and documentation of past illness and family history were documented.

Immediately after admission to critical care unit, blood was drawn for investigation of cardiac biomarkers, complete blood hemogram, serum creatinine values and lipid profile. Blood samples were collected in clot activator vials were sent to laboratory where serum was separated and respective serum indices' levels are estimated. The cardiac biomarkers i.e. CPK-MB and Cardiac troponin- I were estimated using Chemilumiescent technology, by Vitros 250 and Vitros–ECI respectively.

TIMI RISK SCORE:

Thrombolysis in Myocardial Infarction or TIMI Study group was founded by Eugene Braunwald in1984.

This group contributed to TIMI RISK SCORE, which assesses the risk of death and ischemic events in patients experiencing from STEMI, NSTEMI OR UNSTABLE ANGINA.

KILLIP CLASSIFICATION:

KILLIP classification (also known as KILLIP-KIMBALL classification) is used in patients of acute coronary syndrome, taking into account physical examination and the development of heart failure in order to predict and stratify their risk of mortality. This classification was formulated by Dr. Thomas Killip and Dr. John Kimball. This classification helps in grading of risks involved in patients of ACS and the degree of heart failure.

VITROS -ECI

VITROS -250

SYSMEX – TRANSASIA XN-1000

SYSMEX- TRANSASIA XN 350

Statistical analysis

All characteristics were summarized descriptively. For continuous variables, the summary statistics of mean± standard deviation (SD) were used. For categorical data, the number and percentage were used in the data summaries and diagrammatic presentation. Chi-square (χ^2) test was used for association between two categorical variables.

The formula for the chi-square statistic used in the chi square test is:

$$\chi_c^2 = \sum \frac{(O_i - E_i)^2}{E_i}$$

The difference of the means of analysis variables between two independent groups was tested by unpaired t test.

The t statistic to test whether the means are different can be calculated as follows:

$$t = \frac{(\overline{x_1} - \overline{x_2}) - (\mu_1 - \mu_2)}{\sqrt{\frac{s_1^2}{n_1} + \frac{s_2^2}{n_2}}}$$

where $\bar{x}_1$ = mean of sample 1

$\bar{x}_2$ = mean of sample 2

n_1 = number of subjects in sample 1

n_2 = number of subjects in sample 2

s_1^2 = variance of sample 1 = $\frac{\Sigma(x_1 - \bar{x}_1)^2}{n_1}$

s_2^2 = variance of sample 2 = $\frac{\Sigma(x_2 - \bar{x}_2)^2}{n_2}$

The difference of the means of analysis variables between more than two independent groups was tested by ANOVA and F test of testing of equality of Variance.

ANOVA

Source	d.f.	SS	MS	F
Treatment	$a-1$	SS_{treat}	$\frac{SS_{treat}}{a-1}$	$\frac{MS_{treat}}{MS_{error(a)}}$
Error (a)	$N-a$	$SS_{error(a)}$	$\frac{SS_{error(a)}}{N-a}$	
Time	$t-1$	SS_{time}	$\frac{SS_{time}}{t-1}$	$\frac{MS_{time}}{MS_{error(b)}}$
Treat x Time	$(a-1)(t-1)$	$SS_{treat\ x\ time}$	$\frac{SS_{treat\ x\ time}}{(a-1)(t-1)}$	$\frac{MS_{treat\ x\ time}}{MS_{error(b)}}$
Error (b)	$(N-a)(t-1)$	$SS_{error(b)}$	$\frac{SS_{error(b)}}{(N-a)(t-1)}$	
Total	$Nt-1$	SS_{total}		

Bivariate correlation analysis using Pearson's correlation coefficient (r) was used to test the strength and direction of relationships between the interval levels of variables. ROC analysis for Sensitivity- specificity was done to check relative efficiency.

sensitivity or true positive rate (TPR)

eqv. with hit rate, recall

$$TPR = TP/P = TP/(TP + FN)$$

specificity (SPC) or true negative rate

$$SPC = TN/N = TN/(FP + TN)$$

precision or positive predictive value (PPV)

$$PPV = TP/(TP + FP)$$

negative predictive value (NPV)

$$NPV = TN/(TN + FN)$$

If the p-value was < 0.05, then the results were considered to be statistically significant otherwise it was considered as not statistically significant. Data were analyzed using SPSS software v.23.0. and Microsoft office 2007.

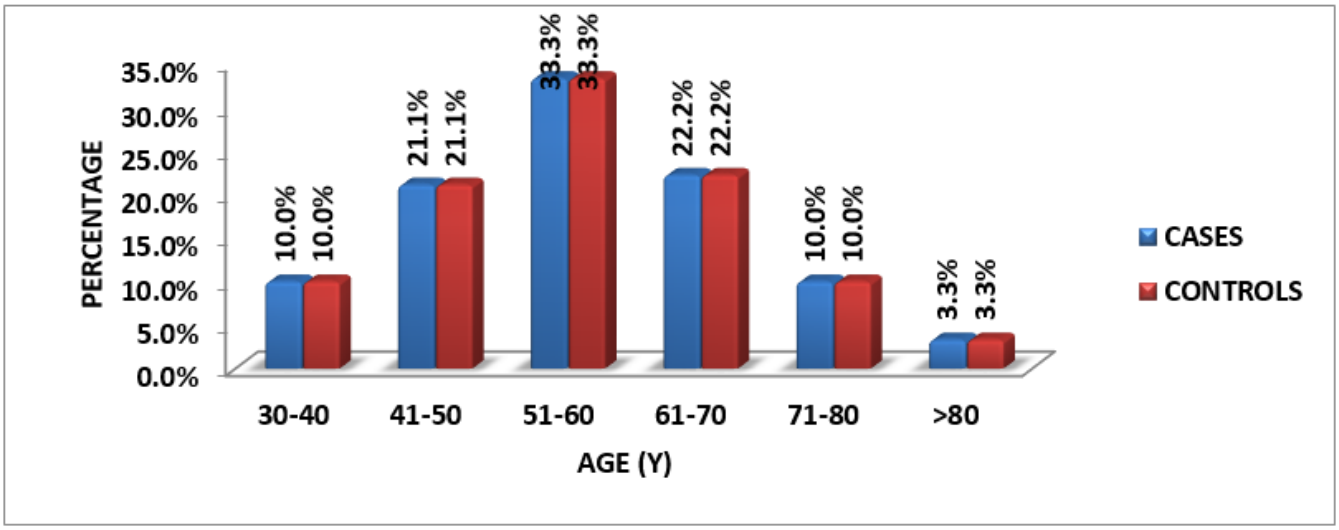
RESULTS

RESULTS

Table: Distribution of patients and controls according to age and sex:

AGE (Y)	MALE		FEMALE		p value
	N	%	N	%	
30-40	6	10.9%	3	8.6%	0.990
41-50	12	21.8%	7	20.0%	
51-60	17	30.9%	13	37.1%	
61-70	12	21.8%	8	22.9%	
71-80	6	10.9%	3	8.6%	
>80	2	3.6%	1	2.9%	
Total	55	100.0%	35	100.0%	

Graph: Distribution of patients and cases according to age and sex:



This table shows the distribution of patients according to their age in both cases and control groups.

As its clearly demonstrated the majority of the patients were from the group of 41 to 70 years.

Table: Distribution of age between cases and controls

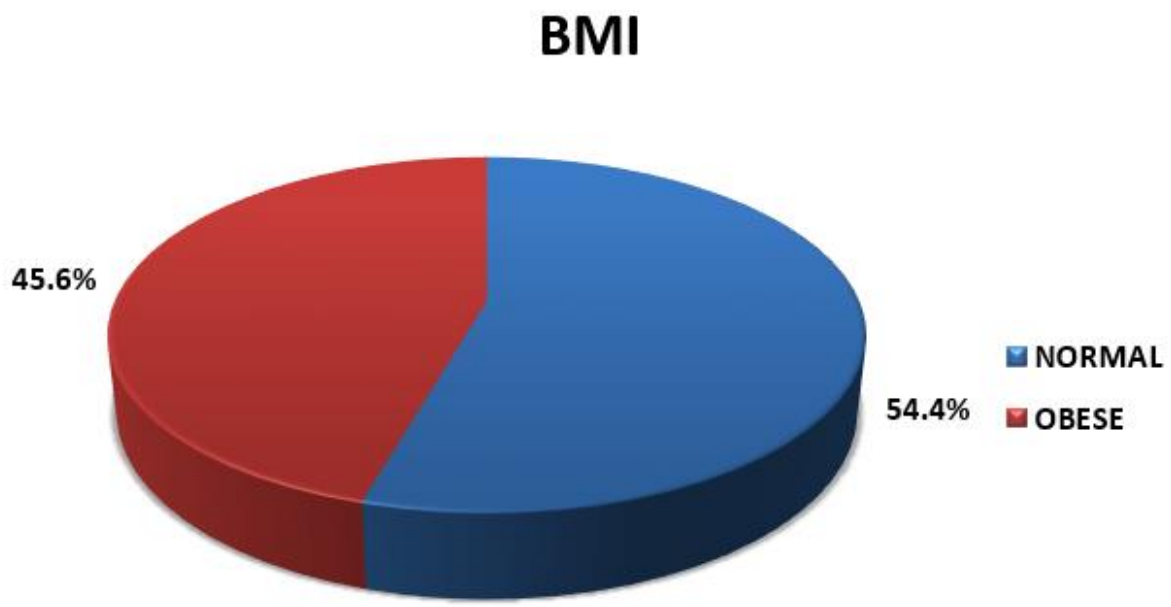
AGE (Y)	CASES		CONTROLS	
	N	%	N	%
30-40	9	10.0%	9	10.0%
41-50	19	21.1%	19	21.1%
51-60	30	33.3%	30	33.3%
61-70	20	22.2%	20	22.2%
71-80	9	10.0%	9	10.0%
>80	3	3.3%	3	3.3%
Total	90	100.0%	90	100.0%

Table: Distribution of cases according to BMI

BMI kg/m^2	N	%
Normal	49	54.4
Obese	41	45.6
Total	90	100.0

Among the 90 cases of Acute coronary syndrome, 45.6% of patients were termed obese according to the BMI Criteria.

Figure: Distribution of cases according to BMI

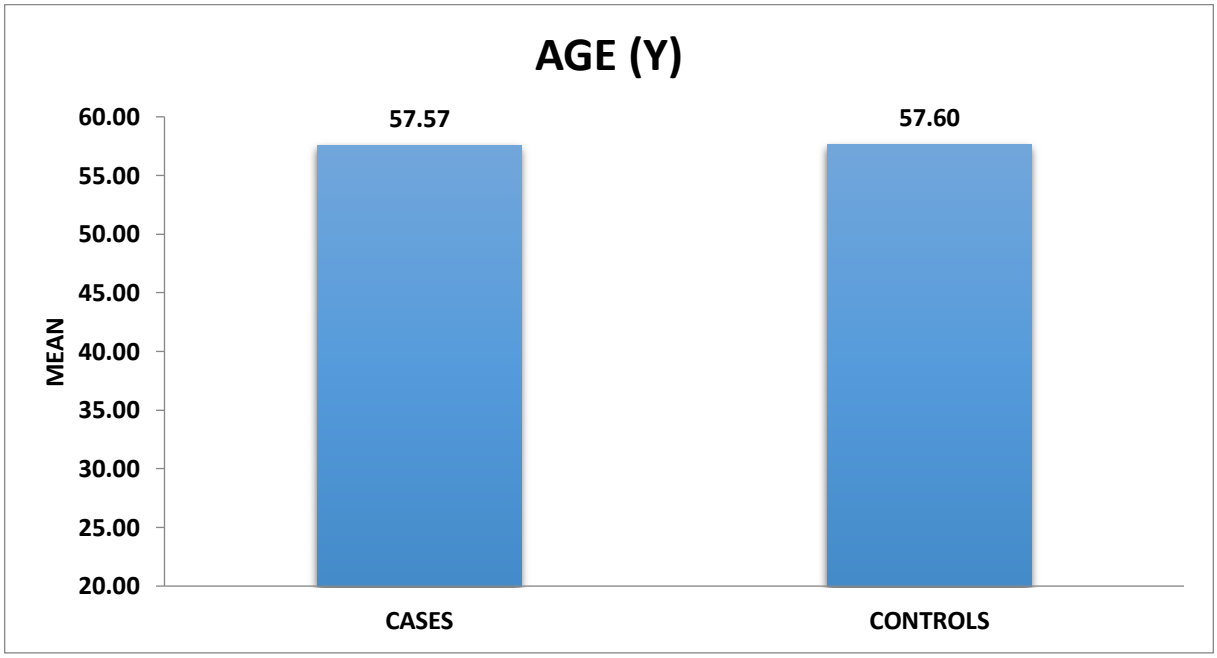


In our study the out of 90 cases of acute coronary syndrome 41 patients were found to be obese and the rest had normal BMI

Table: Mean age between cases and controls

PARAMETERS	CASES		CONTROLS		t value	p value
	Mean	SD	Mean	SD		
Age (Y)	57.57	12.24	57.60	12.25	-0.018	0.985

Figure: Mean age between cases and controls

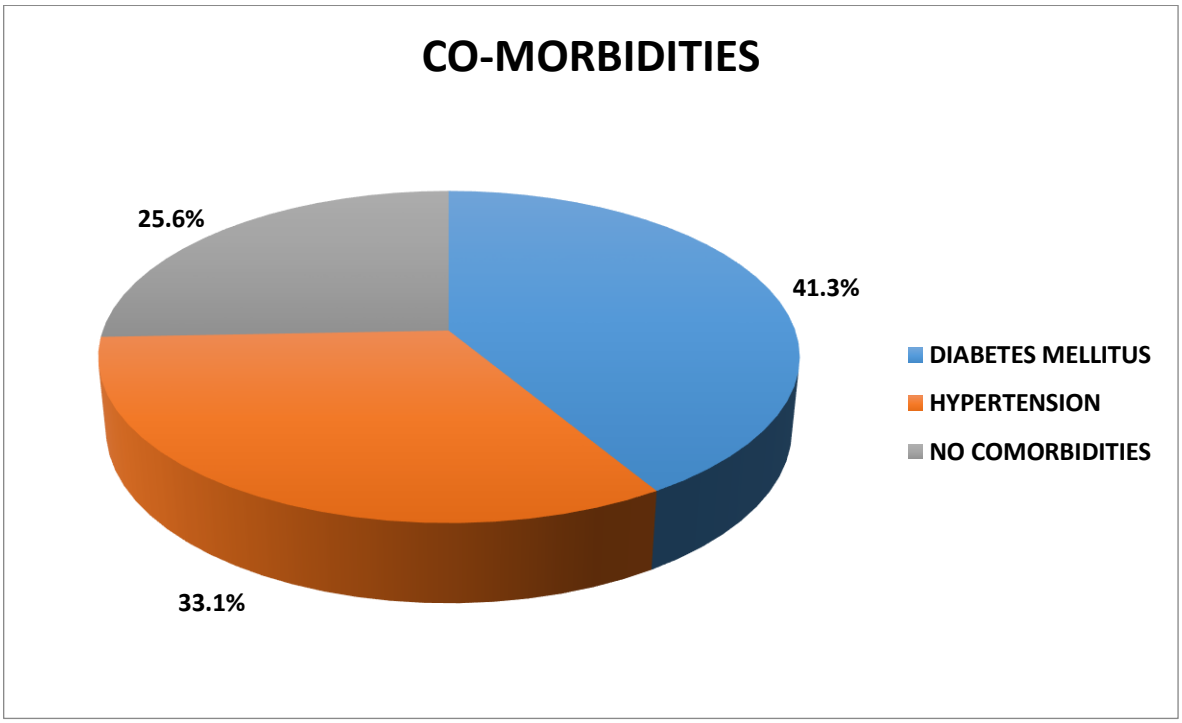


Our study included the age and gender matched controls, this distribution depicts the mean age of 57.57 years and 57.60 years in case and control groups respectively.

Table: Distribution of co-morbidities in cases

CO-MORBIDITIES	N	%
Diabetes mellitus	50	55.6
Hypertension	40	44.4
No co-morbidities	31	34.4

Figure: Distribution of co-morbidities

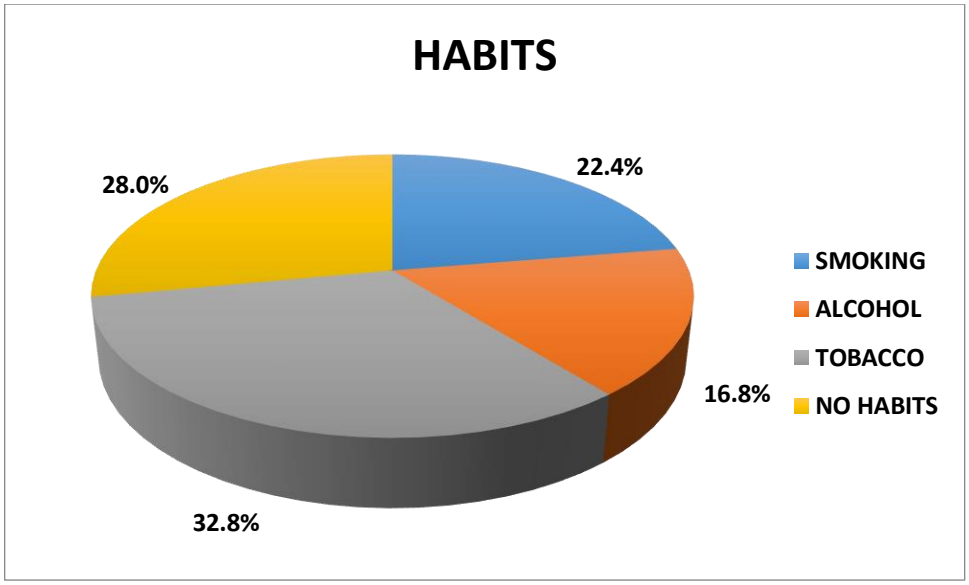


Out of 90 cases of Acute coronary syndrome, 50 patients were diabetic and 40 patients were hypertensive.

Table: Distribution of habits in cases

HABITS	N	%
Smoking	28	31.1
Alcohol	21	23.3
Tobacco	41	45.6
No habits	35	38.9

Figure: Distribution of habits in cases

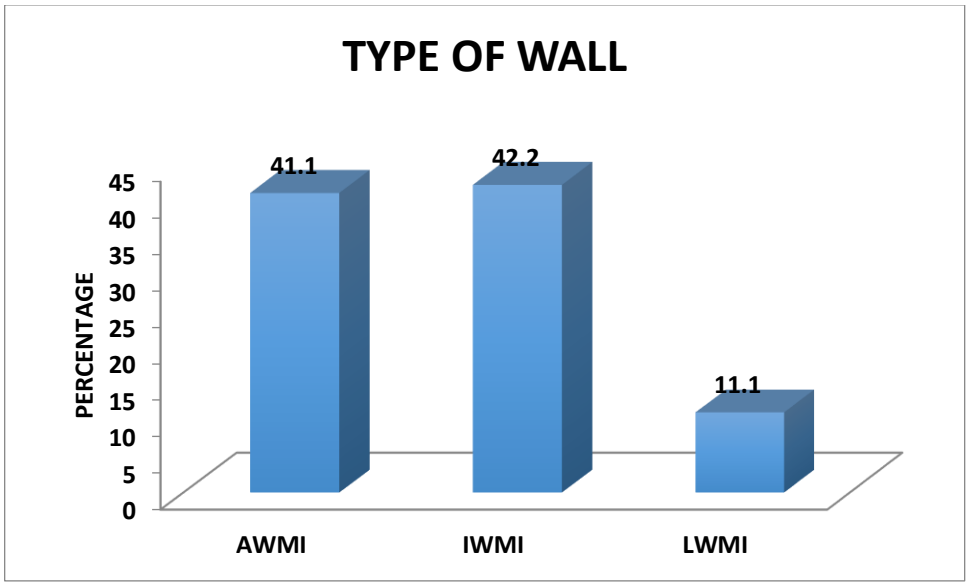


The patients in the cases group were predominantly smokers, followed by 23.3 % of them had a habit of consuming alcohol and 45.6 % patients were tobacco chewers.

Table: Distribution of cases according to type of myocardial wall involved

TYPE OF WALL	NUMBER	%
AWMI	37	41.1
IWMI	38	42.2
LWMI	10	11.1

Figure: Distribution of cases according to type of myocardial wall involved:

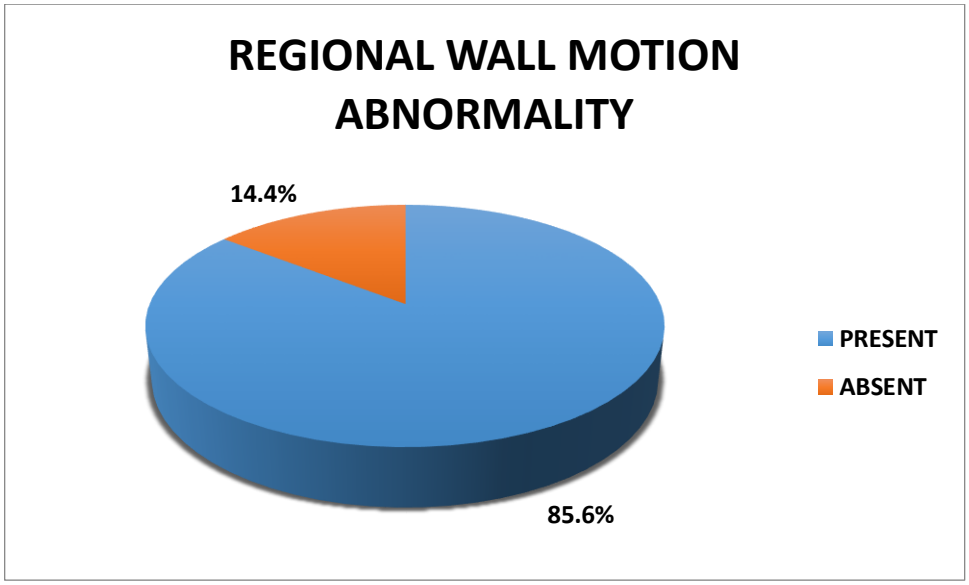


In our study, 41.1 % of cases showed anterior wall of myocardium involvement in MI (AWMI) 42.2 % showed the involvement of inferior wall (IWMI) and the rest 11.1 % had involvement of lateral wall of the myocardium.

Table: Distribution of cases according to regional wall motion abnormality on 2D Echocardiography:

Regional wall motion abnormality	N	%
Present	77	85.6
Absent	13	14.4
Total	90	100

Figure: Distribution of cases according to regional wall motion abnormality

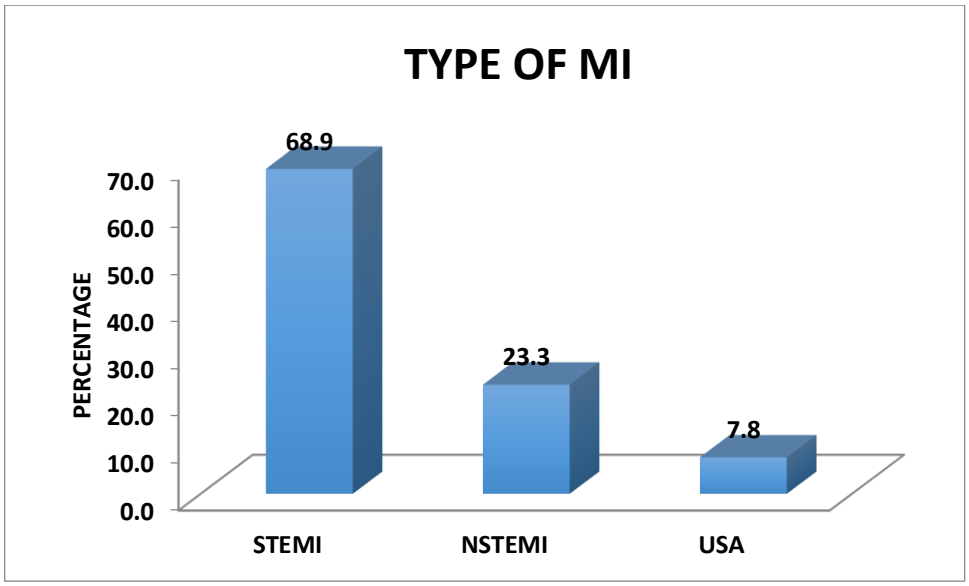


In our study 85.6% of the cases of acute coronary syndrome had presence of Regional wall motion abnormality diagnosed on 2d echocardiography.

Table: Cases according to type of Ischemic Heart Disease:

Type of IHD	N	%
STEMI	62	68.9
NSTEMI	21	23.3
Unstable Angina	7	7.8

Figure: Cases According to Type of Ischemic Heart Disease



In our study, out of 90 cases of acute coronary syndrome, 68.9% cases were of ST elevation MI, 23.3% had Non ST elevation MI and 7.8% of the cases had unstable angina.

Table: Distribution of cases of acute coronary syndrome according to LVEF (%) on 2D Echocardiography:

LVEF (%)	N	%
25-29%	3	3.3
30-34%	21	23.3
35-39%	32	35.6
40-44%	9	10.0
45-49%	18	20.0
50-54%	5	5.6
55-59%	1	1.1
60%	1	1.1
Total	90	100.0

Figure: Distribution of Cases of Acute Coronary Syndrome According to LVEF (%) on 2D Echocardiography

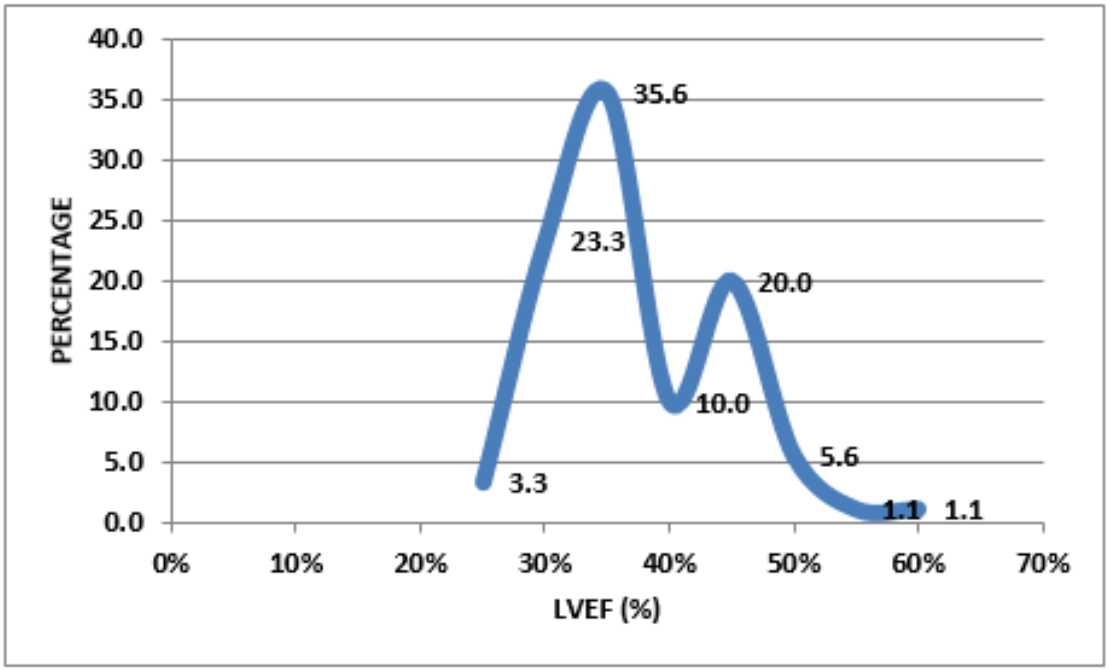
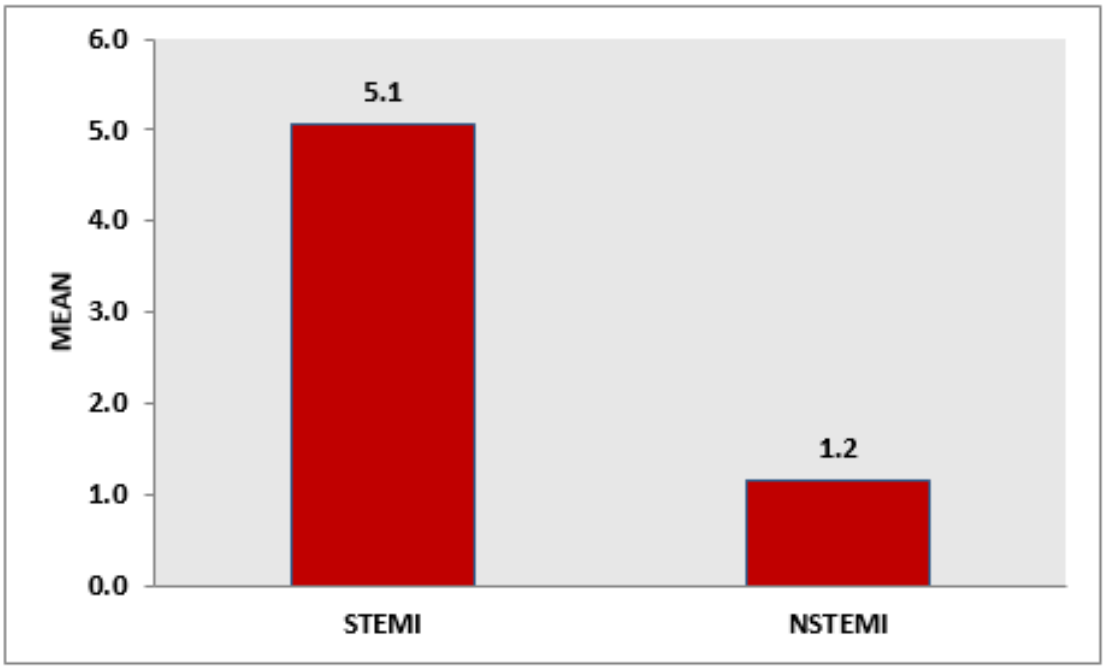


Table: Maximum level of ST elevation and depression in cases

	Minimum	Maximum	Mean	SD
STEMI	0	12mm	5.1	3.7
NSTEMI	0	8mm	1.2	2.2

Figure: Maximum level of ST elevation and depression in cases



This figure depicts the maximum level of ST elevation that was observed in our study i.e. 12mm and ST depressionwas8mm

Table: distribution of biochemical parameters

Biochemical Parameters	Min	Max	Mean	SD
CPK MB (u/L)	15	500	90.1	65.7
Troponin (ng/ml)	45	400	143.9	58.8
Creatinine (mg/dl)	0.7	3	1.5	0.6

This table shows the range of the biochemical parameters observed I the patients of acute coronary syndrome. Mean CPK-MB was 90.1 and Mean Troponin levels were 143.9

Figure: Distribution of Biochemical Parameters

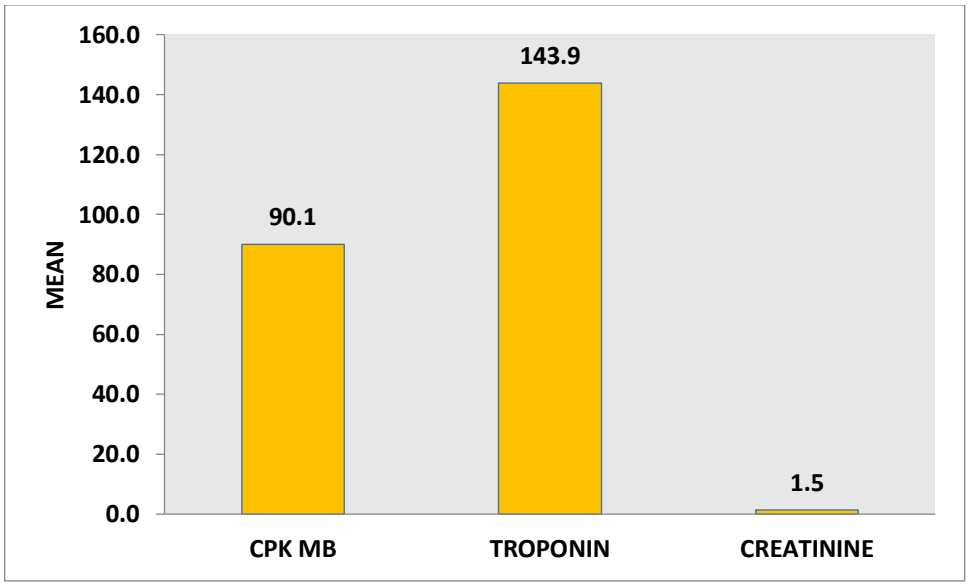


Table: Lipid Profile in Cases of Acute Coronary Syndrome

Lipid Profile	Abnormal		Normal	
	N	%	N	%
Triglycerides (Elevated)	41	45.6%	49	54.4%
Total Cholesterol (Elevated)	56	62.2%	34	37.8%
HDL (Declined)	30	33.3%	60	66.7%
LDL (Elevated)	49	54.4%	41	45.6%
VLDL (Elevated)	21	23.3%	69	76.7%

Figure: Lipid Profile in cases of Acute Coronary Syndrome

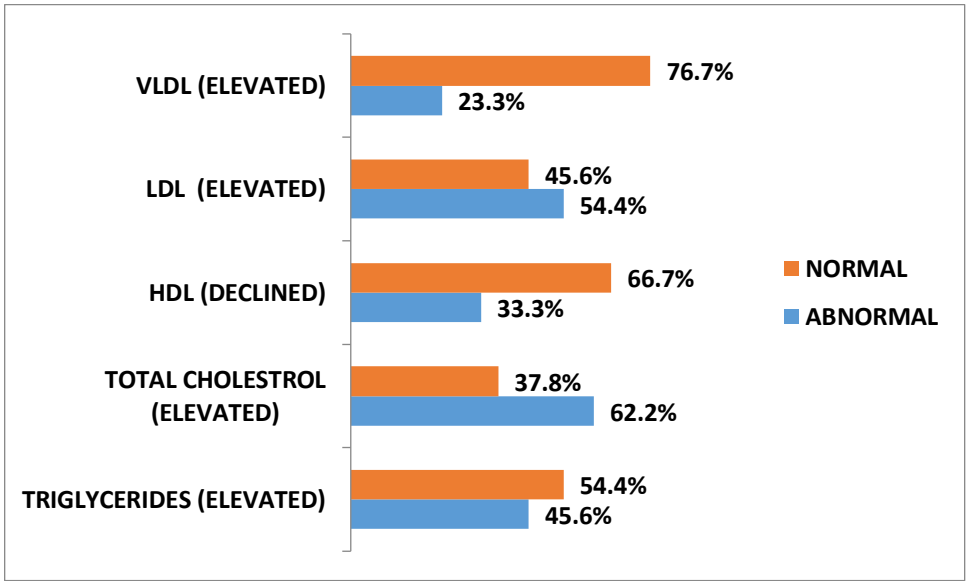


Table: Chief Complaints of Cases

Chief Complaints	N	%
Chest Pain	86	95.6
Sweating	48	53.3
Vomiting	27	30.0
Loose Stools	2	2.2

Figure: Chief Complaints of cases

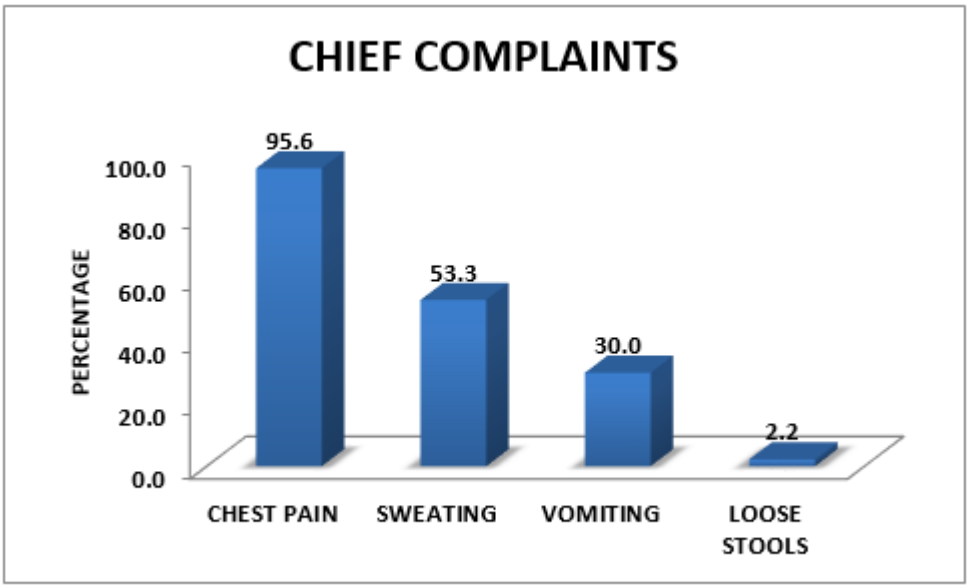
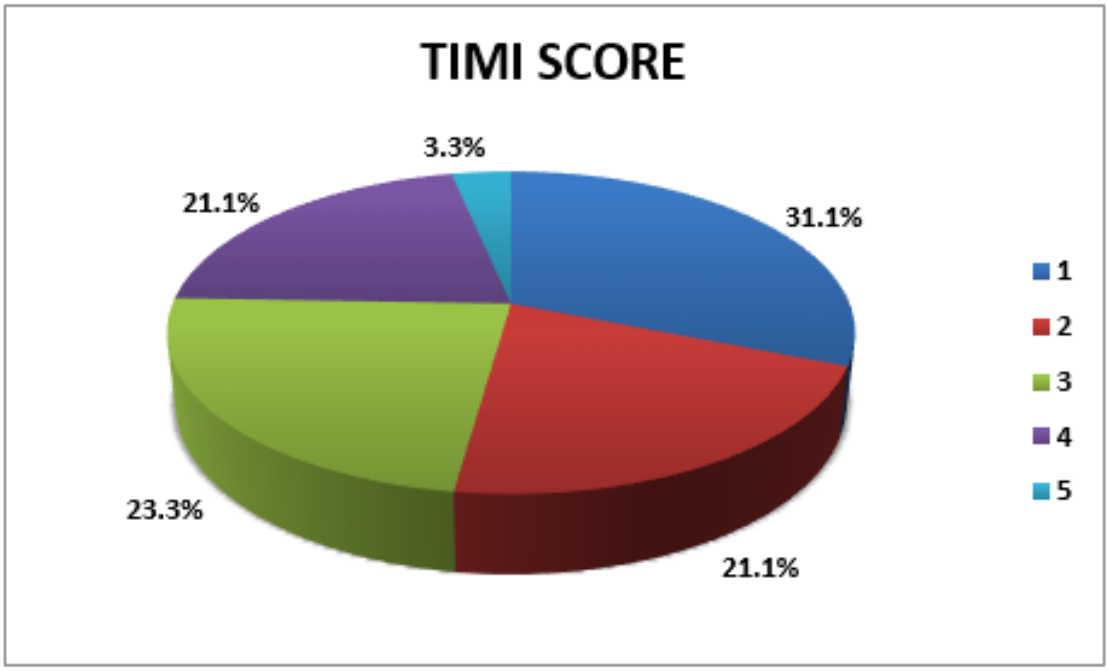


Table: Distribution of TIMI Score

	Minimum	Maximum	Mean	SD
TIMI Score	1	5	2.4	1.2

TIMI Score	N	%
1	28	31.1
2	19	21.1
3	21	23.3
4	19	21.1
5	3	3.3
Total	90	100

Figure: Distribution of TIMI Score

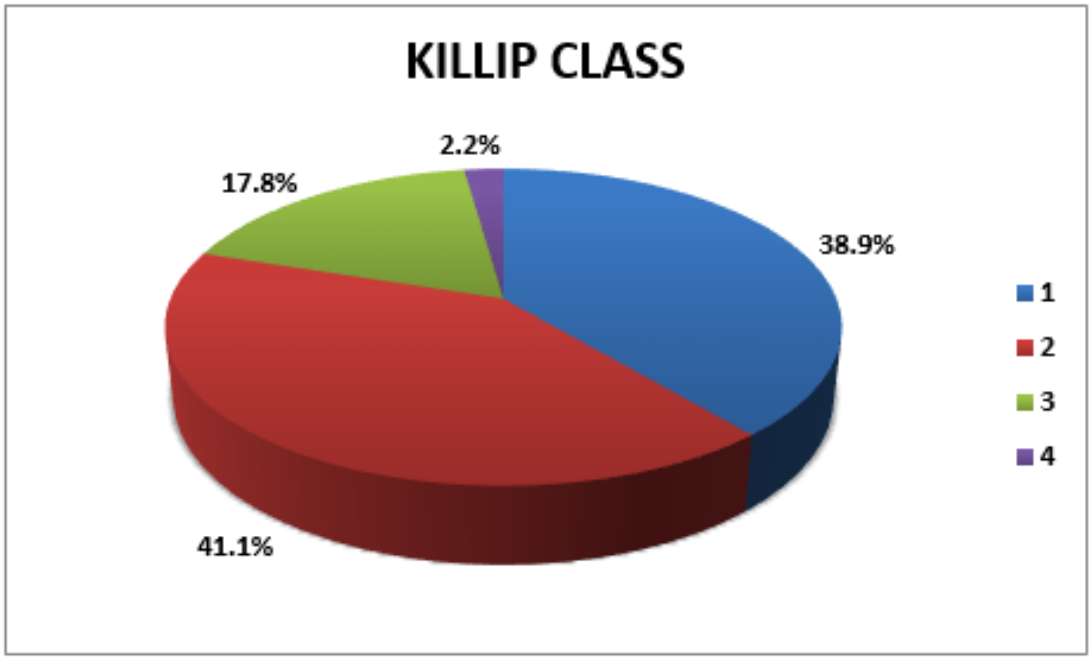


In this study majority of the cases of ACS had TIMI SCORE between 1 to 4, as depicted above .

Table: Distribution of KILLIP Class

KILIP Class	N	%
1	35	38.9
2	37	41.1
3	16	17.8
4	2	2.2
Total	90	100

FIGURE: Distribution KILLIP Class



In this study we observed that, 35 cases of ACS belonged to KILLIP class 1 and 37 belonged to class 2

Table: Distribution of Diastolic Dysfunction in Cases

Diastolic Dysfunction	N	%
Present	73	81.1
Absent	17	18.9
Total	90	100

Figure: Distribution of Diastolic Dysfunction in Cases

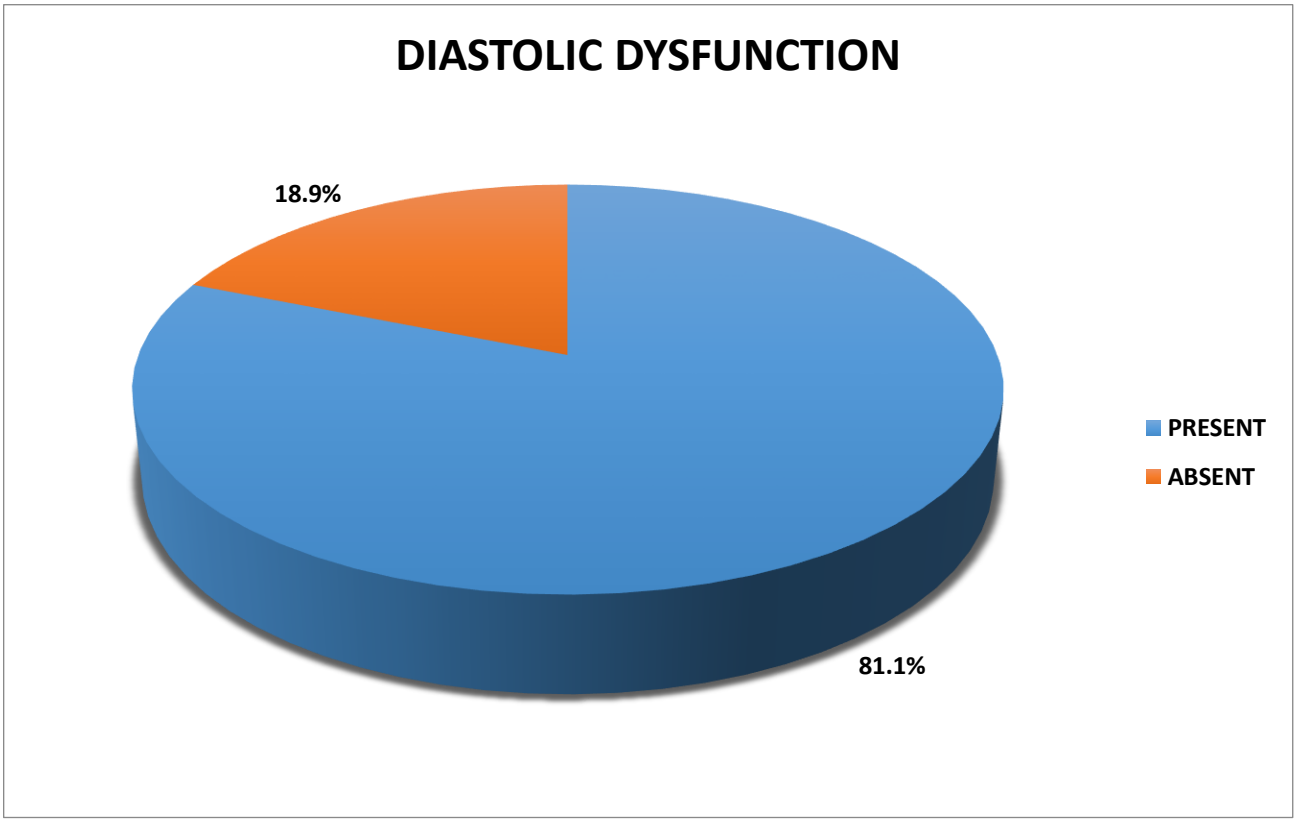


Table: Distribution of Number of Thrombolysis in Cases

Treatment	N	%
Streptokinase	69	76.7
No Thrombolysis	21	23.3
Total	90	100

Figure: Distribution of Treatment in Cases

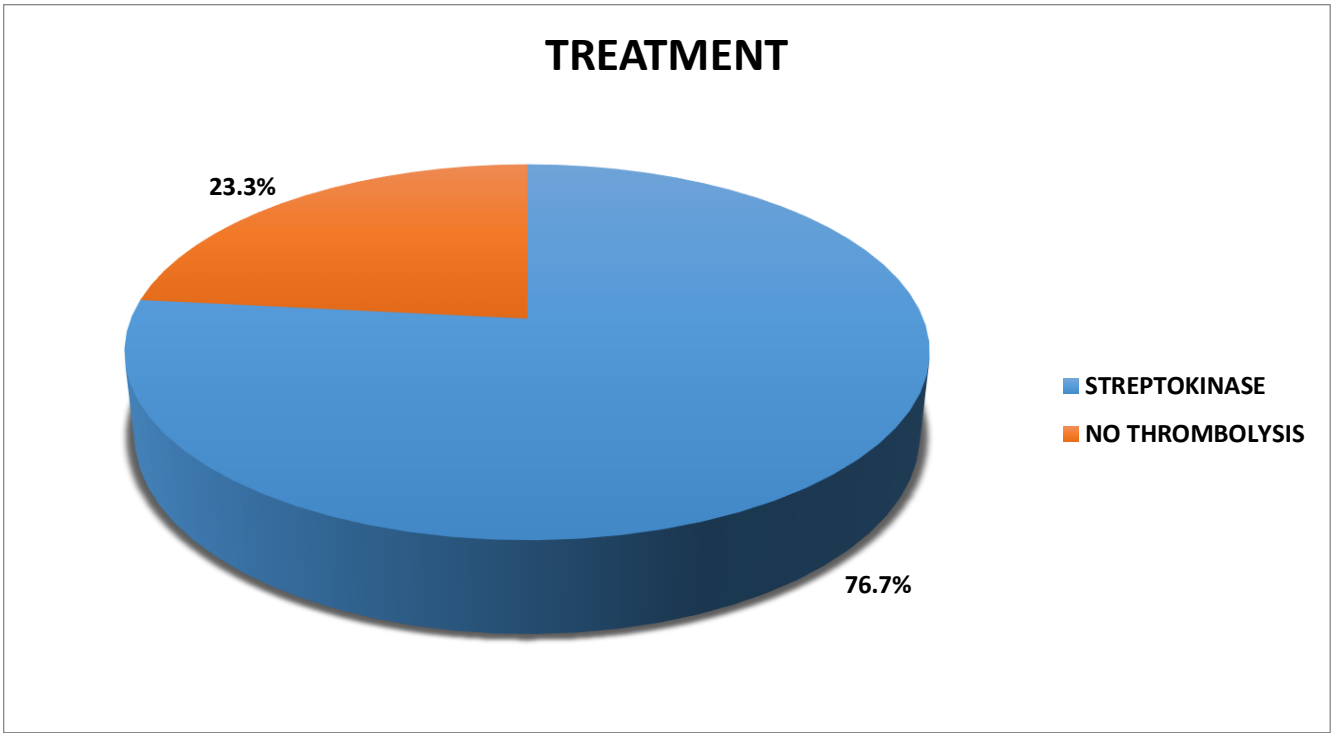
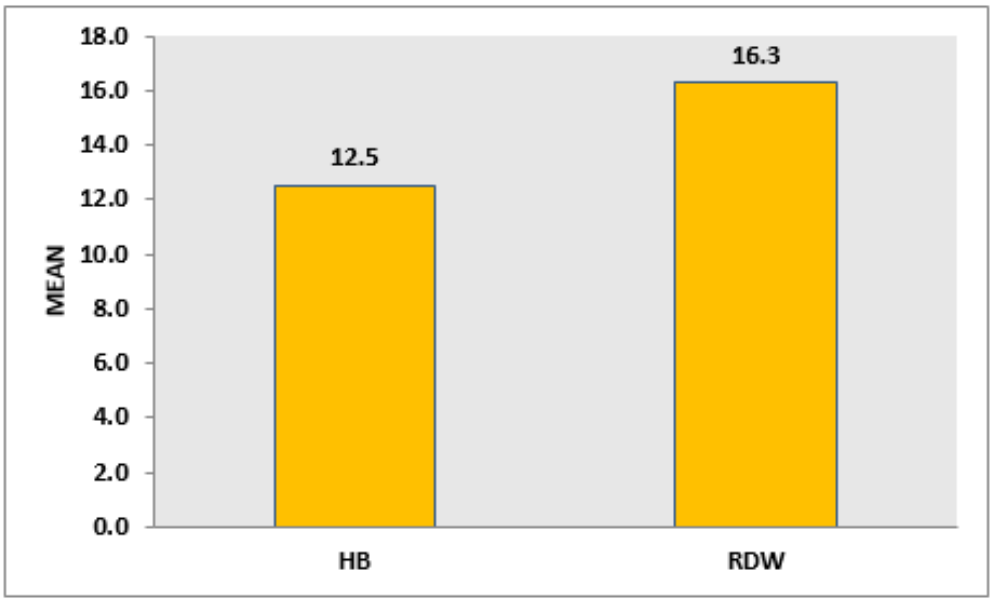


Table: Distribution of Comparison Between Hemoglobin and RDW

	Minimum	Maximum	Mean	SD
HB (gm/dl)	11	17	12.5	1.2
RDW (%)	12	20.8	16.3	1.7

Figure: Distribution of Comparison Between Hemoglobin and RDW



This figure depicts the range of hemoglobin that was observed in our study i.e. 11 to 12.5 g/dl and RDW range was observed to from 12-16.3%

Table: Comparison of Hemoglobin and RDW Between Cases and Controls

Parameters	CASES		CONTROLS		t value	p value
	Mean	SD	Mean	SD		
HB (gm/dl)	12.51	1.17	12.48	1.09	0.164	0.870
RDW (%)	16.29	1.75	11.50	0.91	23.05	<0.001*

Note: * significant at 5% level of significance (p<0.05)

This table shows a comparison between RDW values among cases and controls, as its shown the RDW values are significantly high in cases of MI as compared with that of controls and is statistically significant.

Figure: Comparison of Hemoglobin and RDW Between Cases and Controls

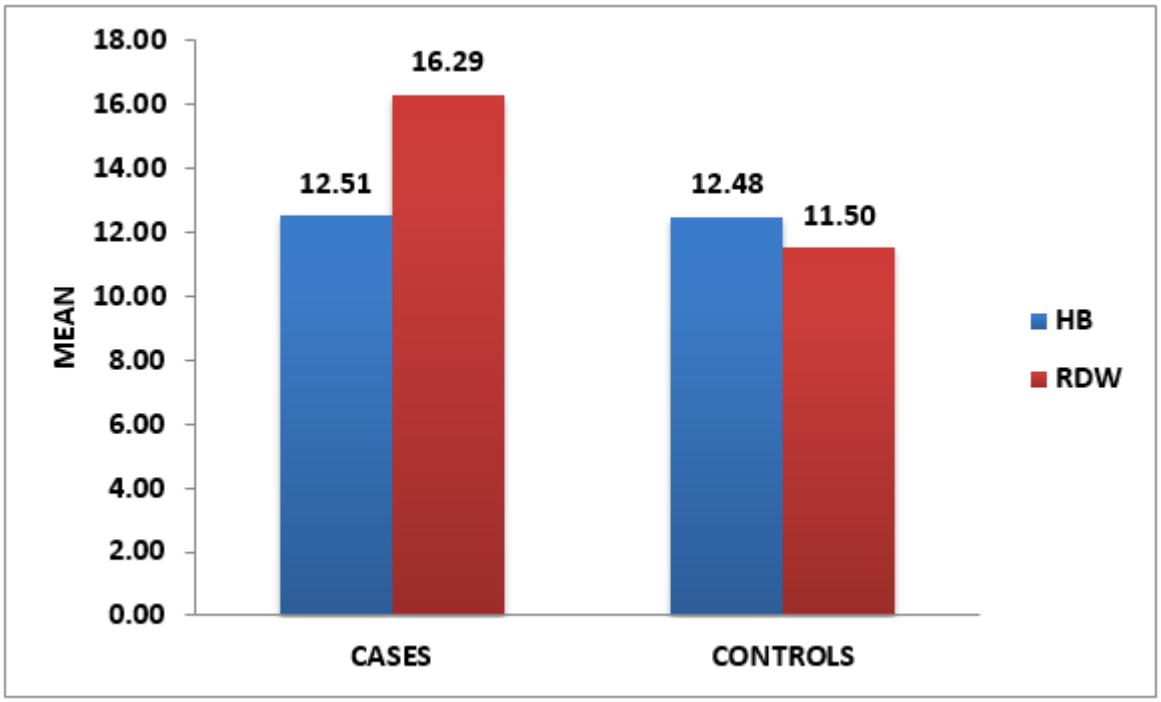


Table: Comparison of Hemoglobin (HB) according to age

HB (gm/dl)	AGE(YRS)						p value
	30-40	40-50	50-60	60-70	70-80	>80	
CASES	12.8±1.23	12.48±1.05	12.69±1.49	12.09±0.78	12.78±0.97	12±0	0.428
CONTROLS	12.59±0.49	12.5±1.15	12.24±1.14	12.76±1.1	12.5±1.23	12.57±1.44	0.722

Figure: Comparison of Hemoglobin (HB) according to age

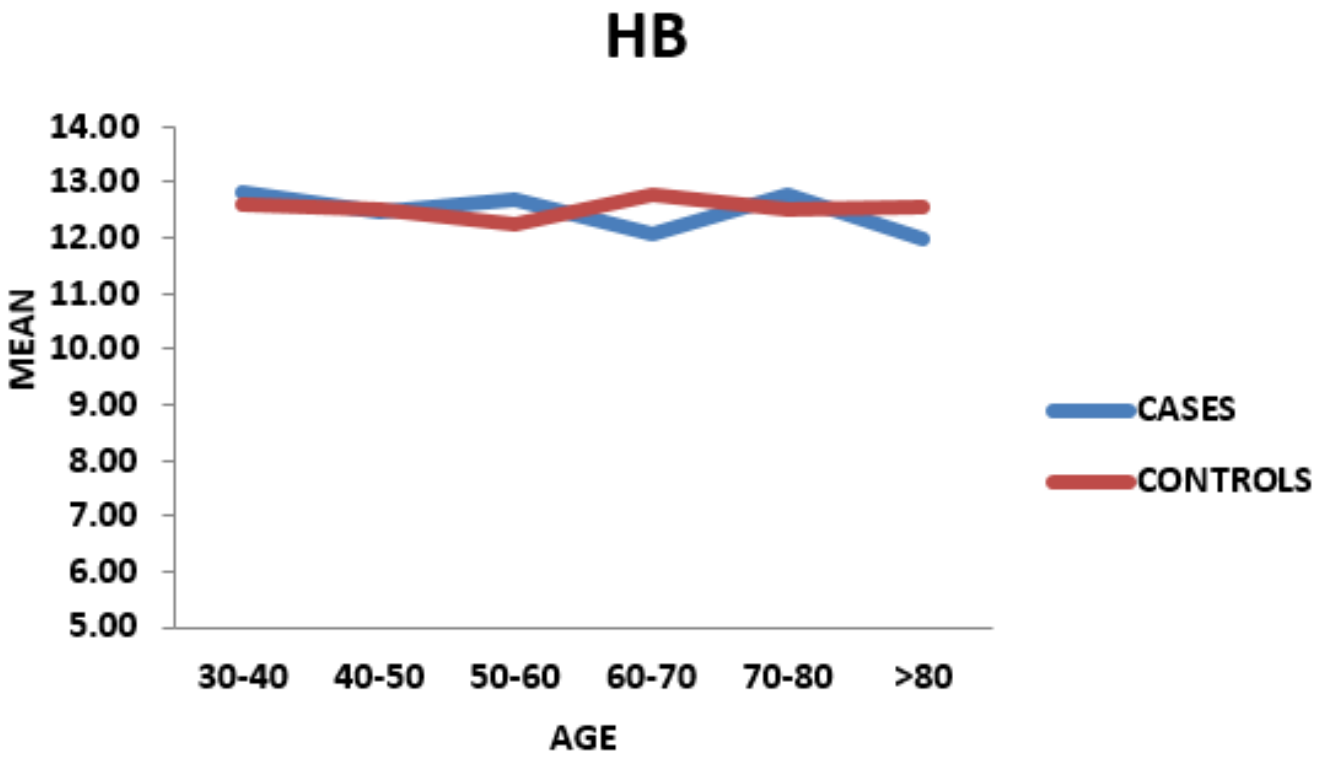


Table: Comparison of RDW according to age

RDW (%)	AGE(YRS)						p value
	30-40	40-50	50-60	60-70	70-80	>80	
CASES	16.58±1.97	16.67±1.47	16.33±1.75	16.25±1.95	16±1.22	13.63±1.48	0.135
CONTROLS	11.6±0.7	11.57±0.89	11.43±0.85	11.5±1.07	11.51±1.06	11.33±1.15	0.993

Figure: Comparison of RDW According to Age

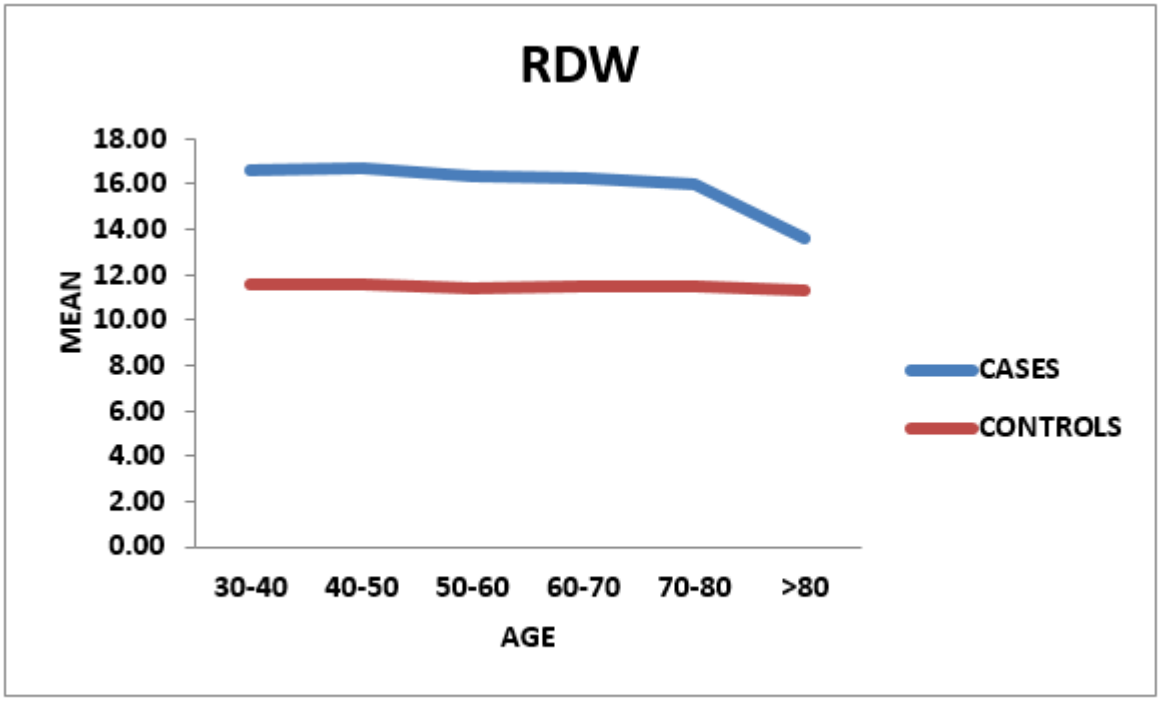


Table: Receiver Operating Characteristic(ROC) Analysis of RDW in Predicting MI

Parameters	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
HB (gm%)	0.503	0.043	0.94	0.418	0.588
RDW (%)	0.99	0.006	<0.001*	0.978	1

Note: * significant at 5% level of significance ($p<0.05$)

Parameters	Positive if Less Than or Equal To	Sensitivity	Specificity
HB	12.05	42.2%	50.0%
RDW	12.95	96.7%	87.8%

According to the table, we can say that with a confidence interval of 95% RDW of 12.95% can be used as cutoff for predicting myocardial infarction with a sensitivity of 96.7% and specificity of 87.8% with area under the curve being 0.978

Figure: Receiver Operating Characteristic(ROC) Analysis of RDW in Predicting MI

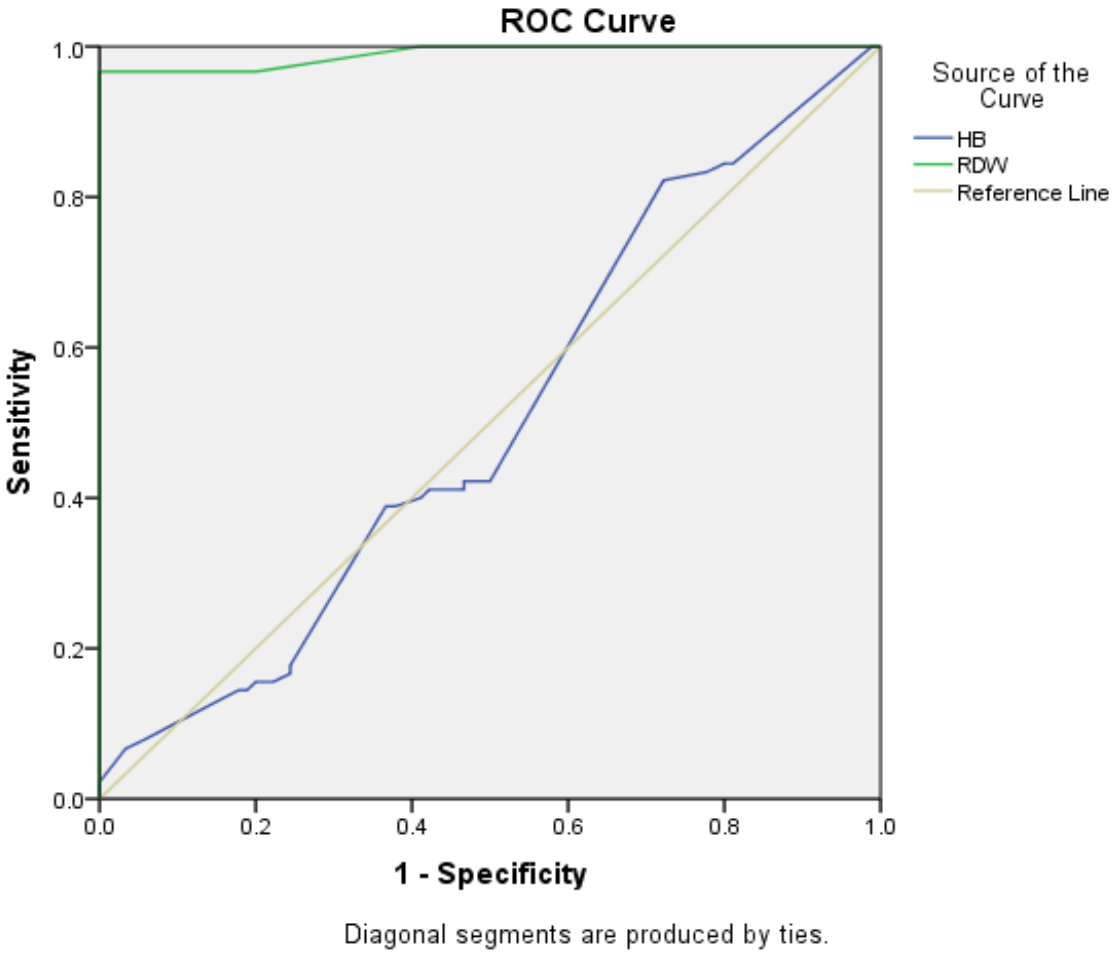
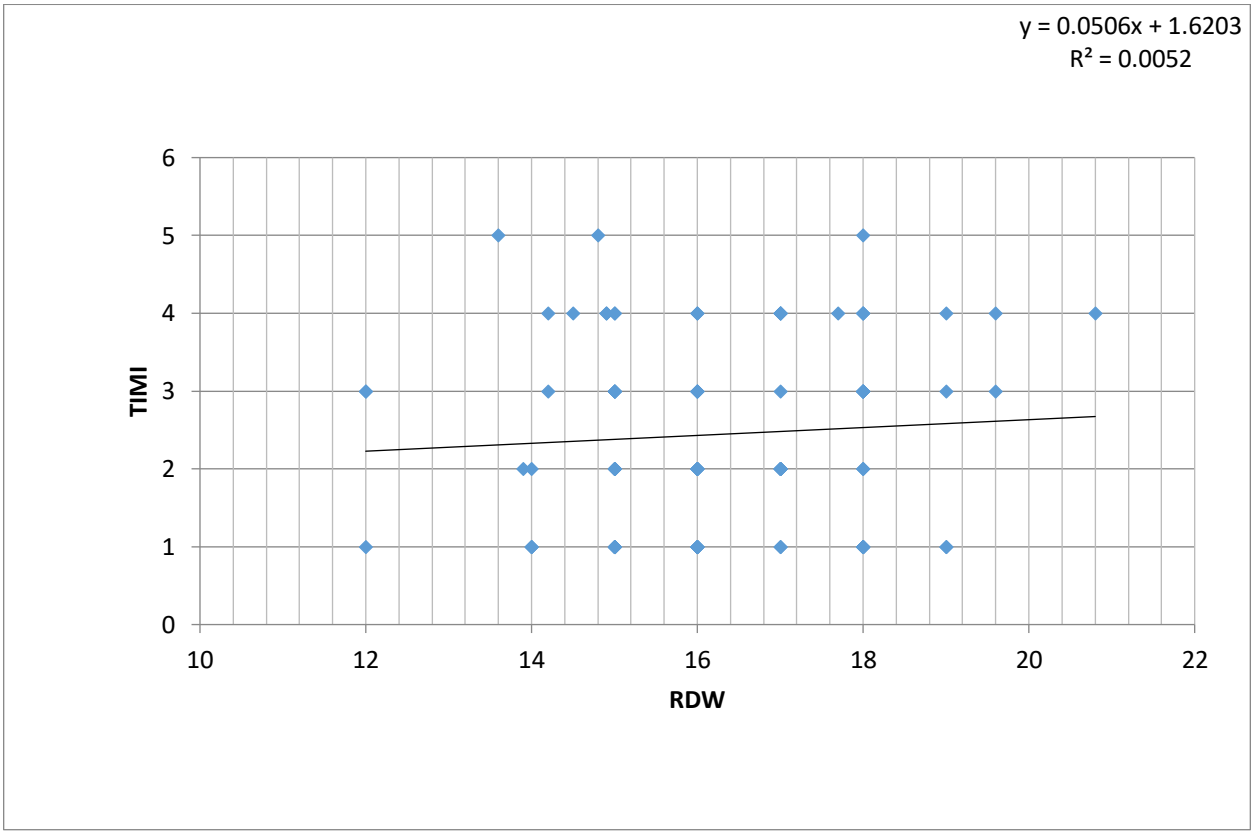


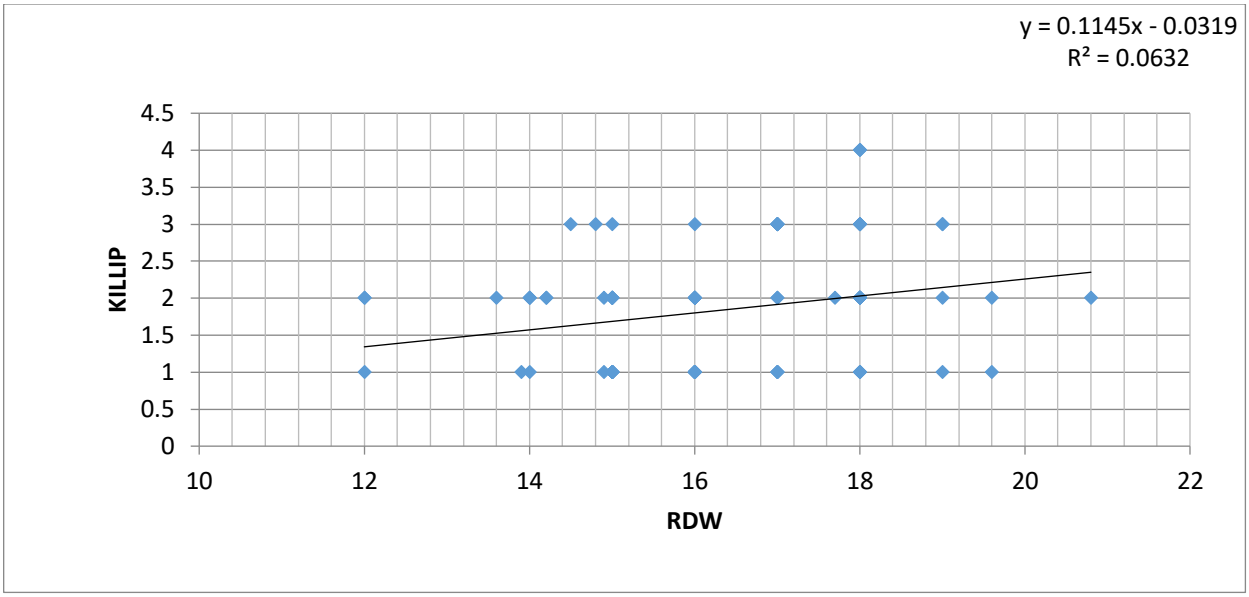
Table: Correlation Between RDW (%) and TIMI SCORE AND KILLIP CLASS

	Correlation Coefficient	p value
TIMI & RDW	0.039	0.715
KILLIP Class & RDW	0.245	0.020*

Note: * significant at 5% level of significance (p<0.05)

Figure: Correlation Between RDW (%) and TIMI SCORE & KILLIP CLASS



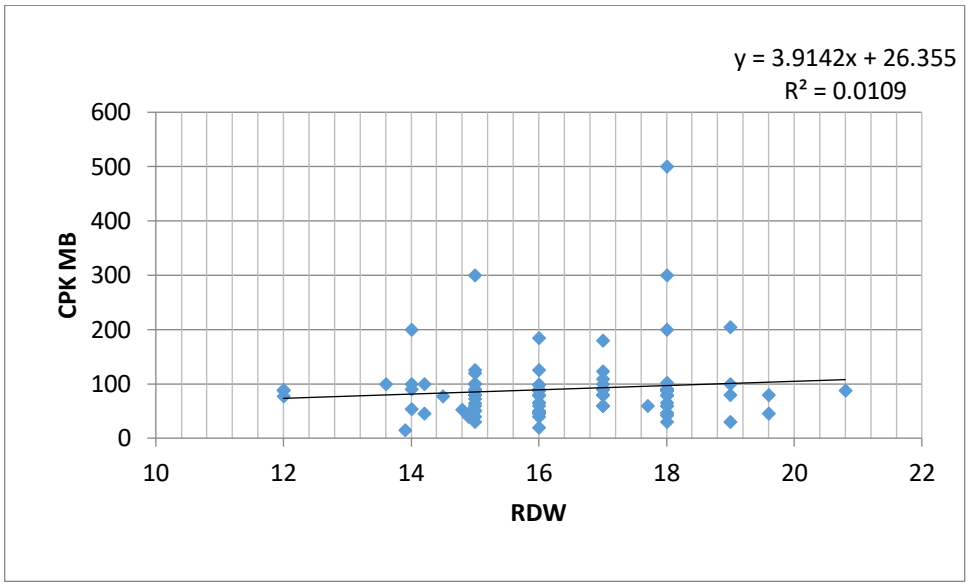


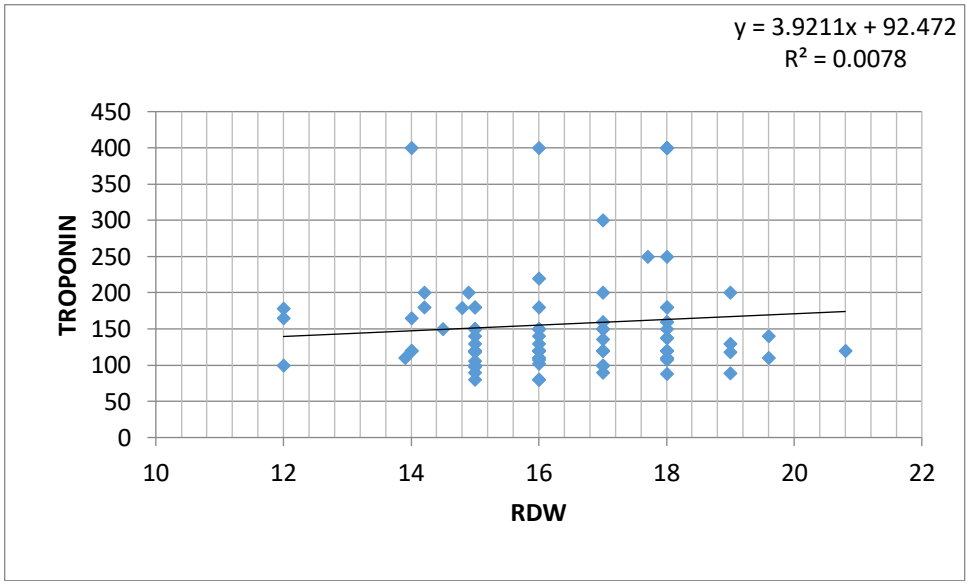
We found a positive correlation between TIMI SCORE and RDW which was not statistically significant but the correlation between KILLIP CLASS and RDW is a strong and positive one which is statistically significant (p=<0.05)

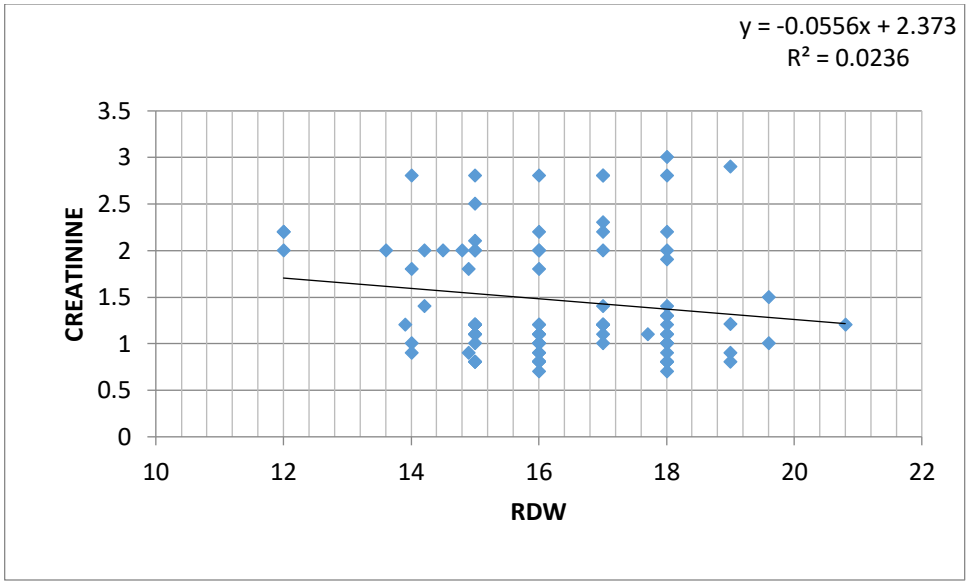
TABLE: CORRELATION BETWEEN RDW AND BIOCHEMICAL PARAMETERS

Biochemical Parameter	**Correlation Coefficient**	**p value**
CPK MB (u/L)	0.104	0.328
Troponin (ng/ml)	0.193	0.478
Creatinine (mg/dl)	-0.154	0.149

Figure: Correlation Between RDW and Biochemical Parameters





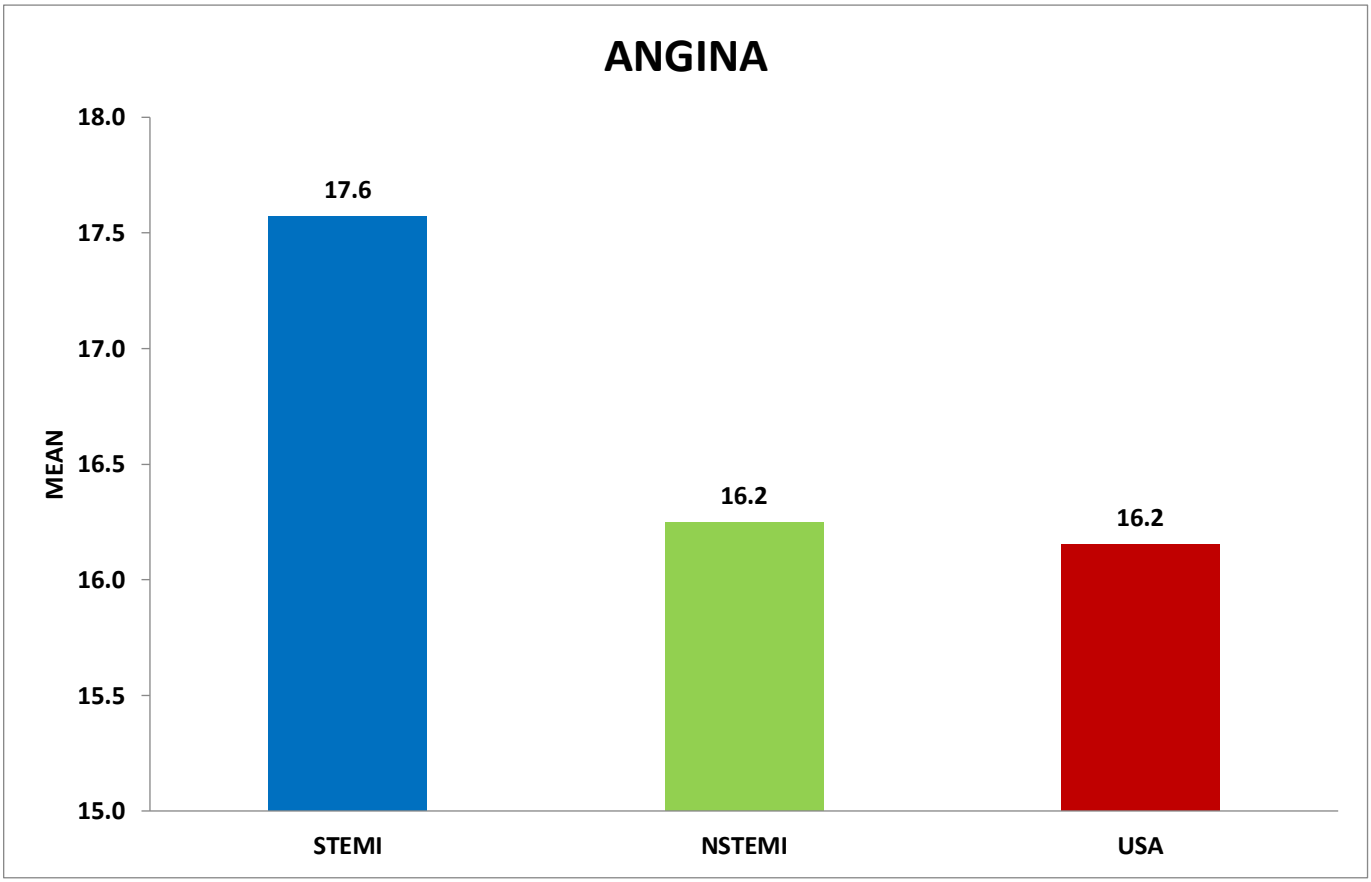


The correlations graphs shown above depict the relation between the RDW values of patients with Acute Coronary Syndrome and Biochemical parameters like CPK-MB, CARDIAC TROPONIN AND CREATININE.

There is definitive positive correlation between RDW and CPK-MB, RDW and CARDIAC TROPONIN values, suggesting that the rise in these parameters also showed elevated levels of RDW in patients. This was not statistically significant.

Table: Correlation between the RDW (%) values and type of Ischemic Heart Disease

RDW (%)	STEMI		NSTEMI		USA		TOTAL		p value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
	17.6	1.0	16.2	2.0	16.2	1.7	16.3	1.7	0.125

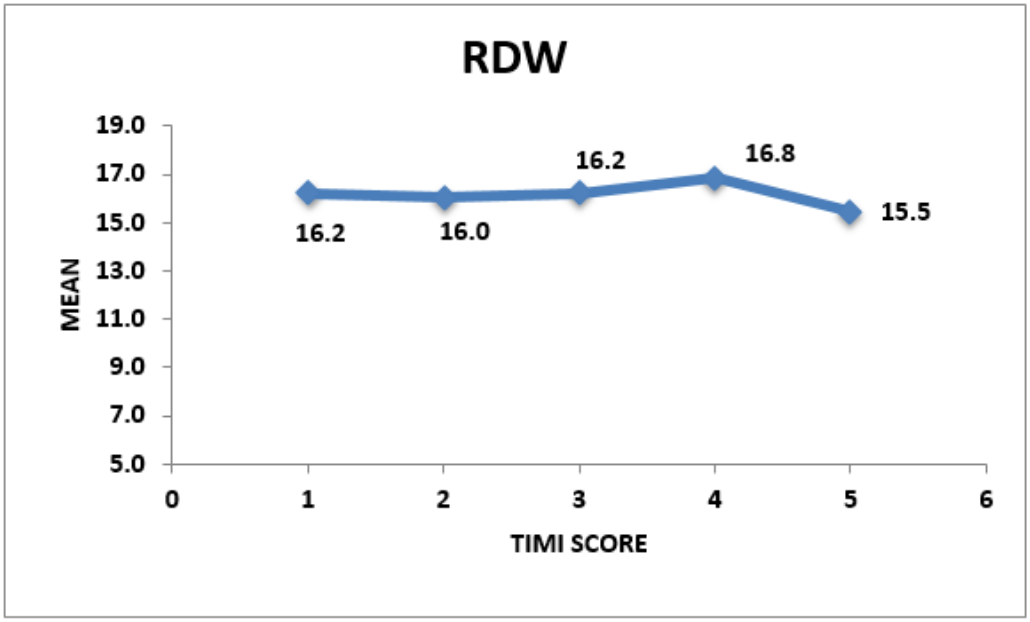


This table shows the correlation between the RDW values and type of myocardial infarction, as depicted above, the RDW values of patients with STEMI are higher than that of NSTEMI and Unstable Angina.

Table: Change in mean RDW (%) according to TIMI Score

TIMI Score	RDW (%)		p value
	Mean	SD	
1	16.2	1.7	0.590
2	16.0	1.2	
3	16.2	2.1	
4	16.8	1.8	
5	15.5	2.3	
Total	16.3	1.7	

Figure: Change in mean RDW (%) according to TIMI Score



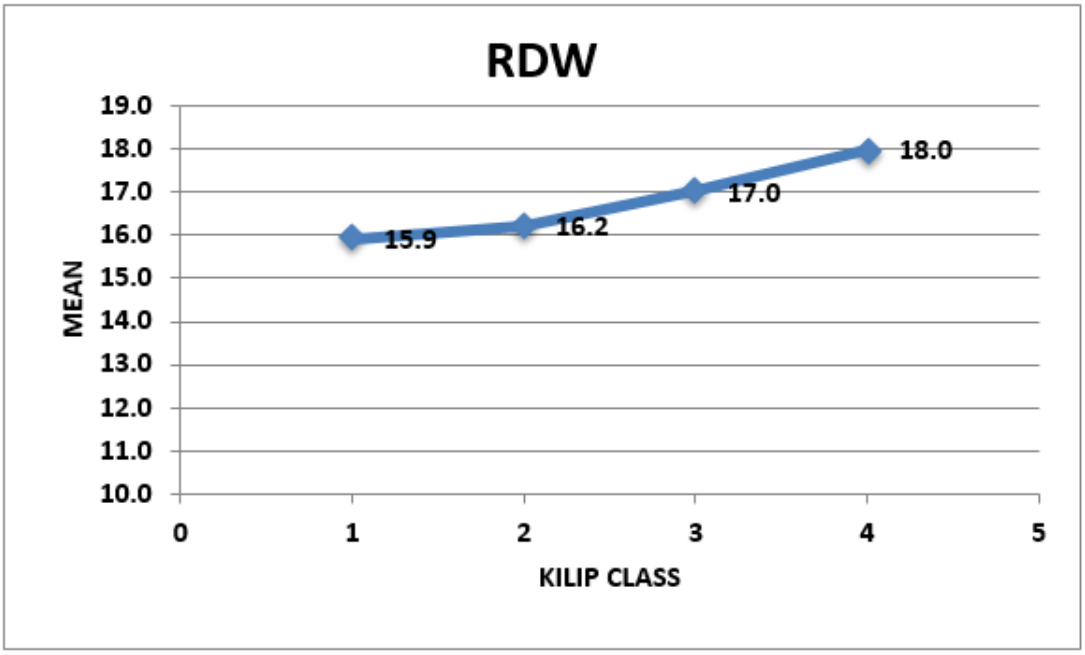
Here, in this study we observed that there is weak positive correlation between RDW and TIMI score, but statistically not significant.

Table: Change in RDW (%) According to KILIP Class

KILIP Class	RDW (%)		p value
	Mean	SD	
1	15.9	1.5	0.047*
2	16.2	2.1	
3	17.0	1.4	
4	18.0	0.0	
Total	16.3	1.7	

Note: * significant at 5% level of significance (p<0.05)

Figure: Change in RDW (%) According to KILLIP Class



This figure clearly depicts that rising RDW values have worsening of KILLIP CLASS, thus suggesting that there is a strong positive correlation and it is statistically significant. (p<0.5)

Table: Change in mean RDW (%) according to 2D Echocardiography parameters

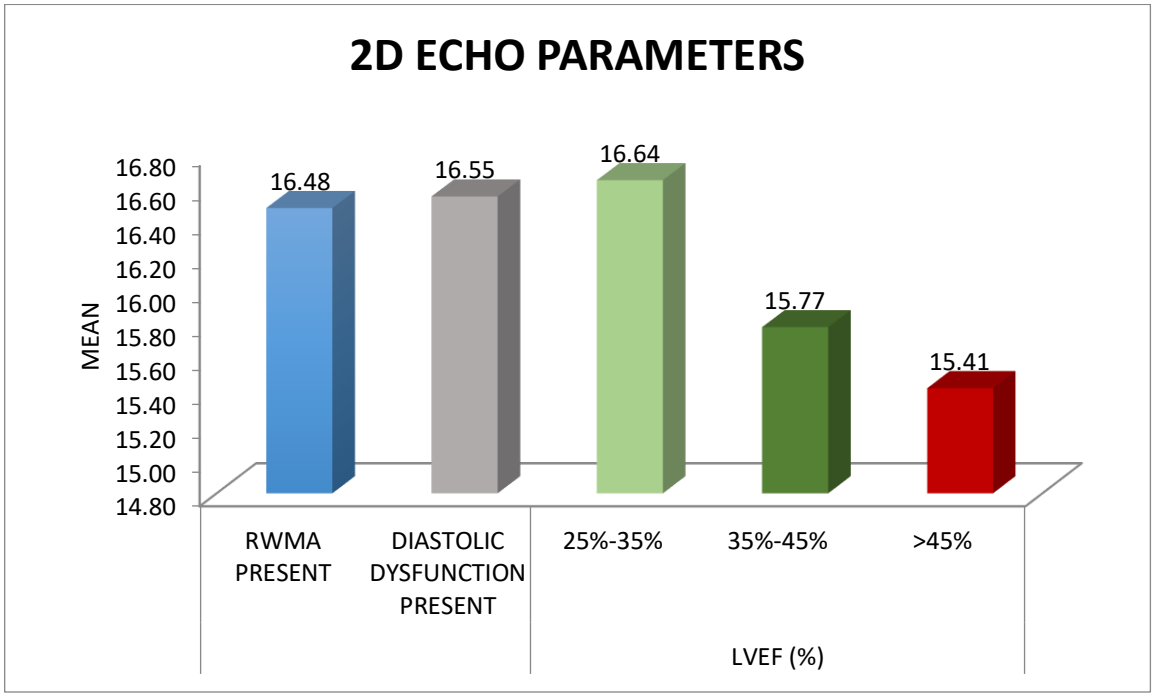
Parameters		RDW		p value
		Mean	SD	
Regional Wall Motion Abnormality	PRESENT	16.48	1.55	0.011*
	ABSENT	15.15	2.41	
Diastolic Dysfunction	PRESENT	16.55	1.59	0.003*
	ABSENT	15.17	2.01	
LVEF (%)	25%-35%	16.64	1.62	0.040*
	35%-45%	15.77	1.67	
	>45%	15.41	2.45	

Note: * significant at 5% level of significance ($p<0.05$)

The table shown above, compares various 2D echocardiography parameters like presence of regional wall motion abnormality (RWMA), Left ventricular ejection Fraction (LVEF) and presence of Diastolic Dysfunction with that of RDW values.

Mean RDW value with presence of RWMA is 16.48% (p=0.011), with presence of diastolic dysfunction it is 16.55% (p=0.003) and poorer left ventricular ejection fraction was seen with higher values of RDW (p=0.04); Thus strongly suggesting a positive correlation between RDW and these 2D Echocardiography parameters and it is statistically significant. This is depicted in the graph below

Figure: Change in mean RDW (%) according to 2D Echocardiography parameters



DISCUSSION

Red cell distribution width (RDW) is an index that is used in measurement of variability of red blood cell size and volume, higher the RDW value indicates higher degree of variability. Regardless of development in effective treatments heart disease remains the foremost cause of mortality and morbidity all around the world. Thus there is an urgent need for assessment of easy, inexpensive, rapid and reliable index for predicting clinical outcomes in patients of acute coronary syndrome and risk of future major cardiac events. As mentioned before anisocytosis i.e. variations in erythrocyte volume, and it may be dependent on not only clinical variables but also on many demographic factors. The erythrocytes of variable size and volume are released from bone marrow under the influence of many factors such as birth season, age physical activity and numerous red blood cell disorders such as anemia related to iron deficiency, folate and B12 deficiency, genetic diseases, (sickle cell anemia, thalassemia), hemolytic anemia and transfusions. [54-56]
The erythropoietin synthesis and erythropoietin hypo-responsiveness are also responsible for anisocytosis and this occurs as a result of increased oxidative stress, presence of inflammation, dyslipidemia, poor nutrition and hypertension. These metabolic abnormalities are often present in patients of acute coronary syndrome, hence there is a strong association between acute coronary syndrome and anisocytosis and is supported by unfailing mechanisms. [57]

There is paucity of studies that report RDW values and its correlation with serum indices in patients of Acute coronary syndrome in Indian scenario. In our study, in patients of ACS, there were 55 males and 35 Females; with 57.57 years and 57.60 years as mean age in cases and controls respectively.

Out of 90 cases of ACS, there were 62 STEMI, 21 NSETMI and 7 unstable anginas. The mean RDW values of patients of ACS in our study was 16.29% and that of controls was 11.50% (p value= <0.001), which is Significantly higher than that of healthy controls and was also comparable to case group of other studies as follows:

SL. No	NAME	RDW CASES	RDW CONTROLS
1.	Guo-dong Cheng et al [2]	13.95%	10.34%
2.	Nagula, karumuri et al [58]	14.59%	13.6%
3.	Our study	16.29%	11.50%

On subgroup analysis, in this study we found that the Cases of ACS, the patients of STEMI had higher Values of RDW as compared to NSTEMI and Unstable angina

TYPE OF MI	RDW VALUES (MEAN)
STEMI	17.6%
NSTEMI	16.2%
UNSTABLE ANGINA	16.3%

This finding is similar to other studies, like Guo-Dong Cheng et al [2] and Naguna Karamuri et al [58] In this study, multivariate regression analysis demonstrated RDW to be an independent predictor of coronary artery disease. Also the Receiver Operating Characteristic (ROC) curve analysis showed that the RDW value of 12.95% is an effective cut off point in diagnosing coronary artery disease with a sensitivity of 96.7% and specificity of 87.8%. Naguna et al [58] had demonstrated that RDW value of 14.3% had specificity of 84.8% in diagnosing Coronary artery disease and Alejandro Rosas-Cabral et al [52] found RDW value of 14.1% to be effective and Akin et al found RDW value of 15.1% as the most significant value associated with higher severity of coronary artery disease. [59] Thus our study shows that effective cut off for RDW is much lower with a better sensitivity and specificity value in diagnosing acute coronary syndromes. However, we would like to add that much work needs to be carried out in establishing an effective and consistent value for RDW in diagnosing ACS Our study also demonstrated a positive correlation between RDW values and TIMI and Killip class, with a p value of 0.020 we reiterated that the patients with higher RDW values had worse TIMI and Killip scores. This finding was consistent with other studies such as, Rosas-Cabral et al. [52] In our study there was positive correlation of RDW values with that of cardiac biomarkers like CPK-MB and Troponin,

(but wasn't statically significant). Thus indicating that greater values of RDW were associated with increased degree of myonecrosis.

In this study we also compared RDW values with that of several 2D Echocardiography parameters like presence of regional wall motion abnormality, left ventricular ejection fraction (LVEF) and diastolic dysfunction. This study demonstrates that the subjects with higher RDW values had reduced LVEF and also had severe hypokinesia of myocardial wall and severe diastolic dysfunction.

CONCLUSION

CONCLUSION

- This study shows that there is a strong correlation between the severity of Acute Coronary syndrome and RDW values.
- There is a positive correlation between the RDW value in predicting AMI and degree of myonecrosis.
- RDW value can be considered as an important, inexpensive parameter of prognosis in patients of AMI.

Limitation of the study:

1. This study has a limited study sample, according to us we need a larger sample size.
2. Patients of acute coronary syndrome with higher RDW values weren't followed up after discharge to assess the mortality in these patients, which according to us could have added more evidence to our study in proving RDW as predictor for mortality.
3. We weren't able to compare RDW values with other inflammatory markers such as, myeloperoxidase, C reactive protein, fibrinogen because these makers aren't routinely obtained in our study population.

SUMMARY

SUMMARY

- This is a hospital based case control study.
- Mean age group of this study is 57.57 years
- Mean RDW value in case is 16.29%, in controls it is 11.50%
- In this study, with 95% of confidence interval RDW of 12.95 % had 96.7% sensitivity and 87.8% specificity in predicting AMI
- Increased value of RDW had poor Killip class and higher TIMI score, which was statistically significant.
- Increased values of RDW had reduced LV ejection fraction statistically significant
- Increased value of RDW had increased cardiac biomarkers suggestive of higher degree of myonecrosis.
- Patients of STEMI had greater values of RDW as compared to that of NSTEMI and unstable angina.

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ANNEXURES

ANNEXURE-I

TIMI UA/NSTEMI RISK SCORE	
1) Age ≥65	1 point
2) ≥3 risk factors for CAD	1 point
3) Use of ASA (last 7 days)	1 point
4) Known CAD (prior stenosis ≥50%)	1 point
5) >1 episode rest angina in <24 h	1 point
6) ST-segment deviation	1 point
7) Elevated cardiac markers	1 point

doi:10.1371/journal.pone.0007947.t001

TIMI STEMI RISK SCORE	
1) Age 65–74/>75	2/3 points
2) Systolic Blood Pressure <100	3 points
3) Heart Rate >100	2 points
4) Killip class II-IV	2 points
5) Anterior STE or LBBB	1 point
6) Diabetes, h/o HTN, or h/o angina	1 point
7) Weight <67 kg	1 point
8) Time to treatment >4 hours	1 point

doi:10.1371/journal.pone.0007947.t002

Killip Class	Definition
I	No evidence of HF
2	Rales up to ½ of lung fields or S3 heart sound, and Systolic BP > 90 mmHg
3	Frank pulmonary edema and Systolic BP > 90 mmHg
4	Cardiogenic shock with rales, Systolic BP < 90 mm Hg and Signs of tissue hypoperfusion

ANNEXURE –III

INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE,

VIJAYAPUR- 586103

TITLE OF THE PROJECT - RED CELL DISTRIBUTION WIDTH VALUE FOR ASSESSMENT OF THE SEVERITY OF ACUTE CORONARY SYNDROME AND ITS CORRELATION WITH SERUM INDICES- A CASE-CONTROL STUDY

PRINCIPAL INVESTIGATOR -

P.G. GUIDE NAME -

CHAIRMAN ETHICAL COMMITTEE

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment

4) BENEFITS:

I understand that my participation in this study will help to patients' survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at any time.

Dr. _____ is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any time without prejudice to my present or future care at this hospital. I also understand that _____may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Dr. Date:

(Investigator)

II) STUDY SUBJECT CONSENT STATEMENT:

I confirm that Dr. _____ has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date:

_____ _____

Witness to signature Date:

APPENDIX –IV

BLDE'S SHRI B.M. PATIL MEDICAL COLLEGE

HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR

Name: CASE NO:

Age: IP NO:

Sex: DOA

: Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past History:

History of diabetes mellitus

History of hypertension

History of immunization:

Personal History:

Diet/appetite:

Sleep:

Bladder and bowel habits:

Smoking/Tobacco chewing/Snuff Inhalation/alcohol:

Family History:

TB: Asthma: Malignancy: DM: HTN:

Treatment History:

General Physical Examination

Height:

Weight:

Body Mass Index:

Vitals

PR:

BP:

RR:

Temp:

Head to toe examination:

SYSTEMIC EXAMINATION.

Respiratory System

Cardiovascular System

Central Nervous System

Per abdomen

INVESTIGATIONS

HAEMATOLOGY –

ECG:

BIOCHEMISTRY:

CPK –MB

C-troponin

Serum electrolytes:

Serum creatinine:

2D ECHO

TIMI SCORE

KILIP CLASS

URINE EXAMINATION -

FINAL DIAGNOSIS

TREATMENT GIVEN