Frequency of inadequate response to thrombolytic in a sample of STEMI patients and their short-term outcome

Research submitted to department of medicine/college of medicine/ Diyala University as a part of M.B.CH .B Graduation requirement.

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All efforts were taken in this project. however, it would not have been possible without the kind support and help of many individuals. I would like to extend my sincere thanks to all of them.

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My thanks and appreciations also go to medical staff in cardiac care unit in baqubah teaching Hospital, who gave me the support in supervene this project , and collecting the patient samples and maintained follow up of the patients throughout admission time .

I would like to express gratitude towards my colleagues for their kind cooperation in collecting the samples .

Abstract

- **Background :** Acute myocardial infarction is a major cause of death throughout the world. Many important advances have become available to Coronary Care Units enabling them to reduce mortality and improve the prognosis, Reperfusion therapy is one of these important advances. thrombolytics remain treatment choice in patient with STEMI when PCI can't be performed within 90-120 minutes from symptoms onset

- **Objectives :** To assess the response of STEMI patients admitted to Baqubah teaching Hospital to the thrombolytic therapy , which is alteplase ,whether failed or done successfully depending on presence one of three criteria involving patient get his symptoms improvement , reduction in amplitude of ST elevation to 50% of initial amplitude , or development of reperfusion arrhythmia , and also to look for short-term outcome of patients receiving this therapeutic agents .

- **Patients and methods :** we do a cross sectional study, that's involved 52 patients with STEMI who were receiving thrombolytic therapy at the time of hospital enrollment who had been admitted in the cardiac care unit . Data used to estimate the frequency of inadequate response to thrombolytic among the involved samples, using ,numbers, percentage ,and Our results can contribute to the general overview regarding the role and extent of success of thrombolytic therapy in management of STEMI and short term outcome. Short term outcome involved that documented during time of hospital admission only , due to difficulties we faced in patients follow up after had been discharged .

- **Results :** In this study , from whole of 52 patients received thrombolytic agent ,which is alteplase , 38 (73%) of them got full response , while 14(27%) of patient failed to get the response. 17(45%) from whole of 38 patients who got successful outcome from thrombolytic therapy presented after 3 hours from symptoms onset , while 9(24%) of these patients presented between 2-3 hours , 8(21%) patients presented within1-2hours , and only 4(11%) patients presented within first 60 minutes .

- **Conclusion :** successful outcome was 73% based on presence one of above mentioned three criteria while failure rates reached to 27% in the enrolled samples. Most of patient got successful management safely and got home discharge , just 1(3%)patient developed complication in form of GIT bleeding controlled well with medically.

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List of abbreviation

ECG	**Electrocardiogram**
STEMI	**ST-elevation myocardial infarction**
PCI	**Percutaneous coronary intervention**
ECHO	**Echocardiography**
EF	**Ejection fraction**
LV	**Left ventricle**
CT SCAN	**Computed tomography Scan**
CPR	**Cardiopulmonary resuscitation**
tPA	**Tissue plasminogen activator**
DM	**Diabetes mellitus**
HT	**Hypertension**
IHD	**Ischemic heart disease**
GIT	**Gastrointestinal tract**
VT	**Ventricular tachycardia**
VF	**Ventricular fibrillation**
ARIC	**Atherosclerosis Risk in Communities Study**

Introduction

Myocardial infarction (MI) is a leading cause of morbidity and mortality in the United States. The estimated annual incidence of MI in the United States is approximately 550,000 new attacks and 200,000 recurrent attacks. (1)

Coronary atherosclerosis is a diffuse process characterized by segmental lesions called coronary plaques. The plaque ruptures, exposing the endothelial lining and allowing prothrombotic enzymes and molecular triggers to mix with the blood. Platelets are activated, and the coagulation cascade is amplified, resulting in a thrombus that occludes the vessel and prevents the circulation of oxygenated blood. Irreversible ischemia-induced myocardial necrosis may occur within 20-60 minutes of occlusion. (2)

STEMI is defined as Myocardial damage with new ST elevation at the J point in at least two contiguous leads of 2 mm (0.2 mV) or more in men or 1.5 mm (0.15 mV) in women in leads V2-V3 and/or 1 mm (0.1 mV) or more in other contiguous limb leads. (3)

The mainstay of treatment is reperfusion therapy involving either administration of fibrinolytics (pharmacologic reperfusion) or primary percutaneous coronary intervention (PCI; ie, mechanical reperfusion).

PCI performed within 90 minutes of a patient's arrival is superior to fibrinolysis with respect to combined endpoints of death, stroke, and reinfarction. Unfortunately, PCI is not widely available at acute care hospitals. (4)

Current guidelines strongly recommend performing primary PCI in patients presenting with symptoms of less than 12 hours' duration, or those who present with cardiogenic shock or who develop acute severe heart failure, irrespective of time of delay from onset of symptoms. Guidelines also recommend considering primary PCI for patients who present between 12 and 24 hours after onset of symptoms, provided there is ongoing clinical or ECG evidence of myocardial ischemia. (5)

Fibrinolytic therapy is a proven treatment for the management of AMI. It is more universally available to patients without contraindications, can be administered by any properly trained health care provider, and can be given in the prehospital setting. Its efficacy declines as the duration of ischemia increases. The goal is a door-to-needle time of less than 30 minutes, and every effort must be made to minimize the time to therapy. Patients older than 75 years derive significant benefit from fibrinolytic therapy, even though their risk of bleeding is higher.

Fibrinolytic agents are given in conjunction with antithrombin and antiplatelet agents, which help to maintain vessel patency once the clot has been dissolved.

Patients receiving thrombolytic therapy must undergo a constant neurologic and cardiovascular evaluation with blood pressure monitoring every 15 minutes during and after tPA infusion for at least 2 hours, then half-hourly for 6 hours and hourly for the next 16 hours after injection. Strict BP monitoring is essential to prevent complications. Thrombolytic therapy should be stopped urgently with any signs of neurologic deterioration, and the patient should receive an emergency computed tomography (CT). [(6)]

Fibrinolytic agents or any anticoagulants must be stopped immediately with any evidence of bleeding complications in a patient with ongoing fibrinolytic therapy. In the next step, supportive measures should be instituted, including volume correction and blood factor transfusion.If the patient also has been on concomitant heparin, protamine sulfate can reverse the heparin effect. [(7)]

Despite the number of agents available and the trials quoted in which these drugs were studied extensively, there are still many areas of controversy – as a result of which, even in a country like the USA, only a quarter to a third of all patients of acute MI actually receive thrombolytic therapy. These areas of controversy include the time window for administering the agent, its use in elderly patients, in patients with non-Q MI and unstable angina, in patients with non-diagnostic ECGs and the optimal adjunctive therapy.

The earliest trial which looked into the time-window question was the GISSI trial [7]. In this study, patients were enrolled up to 12 hours of onset of chest pain and benefit was shown to be a direct function of the time lapse from the onset of pain. The benefit for patients reporting beyond 6 hours was not found to be statistically significant. This report led to the recommendation for the use of thrombolytic agents only within the first 6 hours. The more recent GUSTO trial also only included patients who came within the first 6 hour time frame [(8)]However, other studies such as the LATE trial [(9)]and the EMERAS report [(10)]considered patients reporting beyond this time frame. Thus, in the LATE trial using alteplase (rt-PA) there was significant reduction in mortality even in patients receiving the drug after 6 hours (8.9% vs 11.97% for placebo) but with a smaller reduction if given beyond 12 hours. The EMERAS study reported a definite but non-significant trend towards lower mortality with SK in patients given the drug between 7–12 hours and no improvement if given after that period. Based on these observations, it would be wise to recommend thrombolytic therapy to patients reporting within 12 hours of onset of chest pain.

Fibrinolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms of STEMI, and much of this benefit is maintained for at least 10 years. When appropriately used, fibrinolytic therapy appears to reduce infarct size, limit LV dysfunction, and reduce the incidence of serious

complications such as septal rupture, cardiogenic shock, and malignant ventricular arrhythmias. Since myocardium can be salvaged only before it has been irreversibly injured, the timing of reperfusion therapy, by fibrinolysis or a catheter-based approach, is of extreme importance in achieving maximum benefit. While the upper time limit depends on specific factors in individual patients, it is clear that every minute counts and that patients treated within 1–3 h of the onset of symptoms generally benefit most.

Although reduction of the mortality rate is more modest, the therapy remains of benefit for many patients seen 3–6 h after the onset of infarction, and some benefit appears to be possible up to 12 h, especially if chest discomfort is still present and ST segments remain elevated. Compared with PCI for STEMI (primary PCI), fibrinolysis is generally the preferred reperfusion strategy for patients presenting in the first hour of symptoms, if there are logistical concerns about transportation of the patient to a suitable PCI center (experienced operator and team with a track record for a "door-to-balloon" time of <2 h), or there is an anticipated delay of at least 1 h between the time that fibrinolysis could be started versus implementation of PCI.

Mechanism of thrombolytic drugs Action

Hemostasis and thrombosis result from an integrated and interactive response of the coagulation factors, blood vessels, and platelets. During thrombosis, circulating prothrombin is converted to its active form thrombin by activated platelets. Active thrombin then converts the fibrinogen into fibrin with the eventual formation of a fibrin matrix. This process is counterbalanced by plasmin derived from plasminogen, which gathers in the fibrin matrix. Tissue plasminogen activator (tPA) is a natural fibrinolytic found in endothelial cells. It shows fibrin specificity and affinity. The end goal of this therapy is to convert plasminogen into plasmin which is accomplished at the location of the thrombus and on the surface of fibrin by the binding of tPA to plasminogen. This binding helps the conversion. (5)

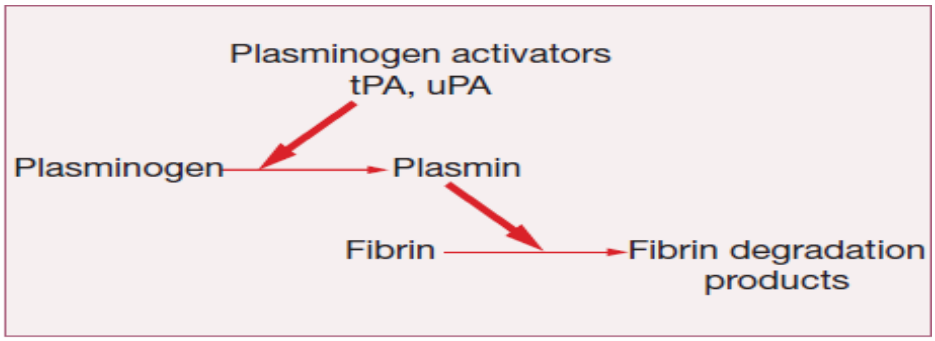


Fig. 29.3 The blood fibrinolytic system. tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator.

Thrombolytic therapy can be subdivided into two categories which are as follows:

- Fibrin-specific agents: These agents mostly need the presence of fibrin for the conversion, but on a minimal scale can do so in the absence of fibrin too. e.g. alteplase (tPA), reteplase (recombinant plasminogen activator [r-PA]), and tenecteplase
- Non-fibrin-specific agents: These do not need fibrin presence for conversion, which is why they can do this systemically. e.g., streptokinase

Contraindications of Thrombolytic therapy

There is absolute contraindications for fibrinolytic use in STEMI include the following: [11] Prior intracranial hemorrhage (ICH), Known structural cerebral vascular lesion , Known malignant intracranial neoplasm , Ischemic stroke within 3 months , Suspected aortic dissection, Active bleeding or bleeding diathesis (excluding menses), Significant closed head trauma or facial trauma within 3 months, Intracranial or intraspinal surgery within 2 months , Severe uncontrolled hypertension (unresponsive to emergency therapy), For streptokinase, prior treatment within the previous 6 months.

The relative contraindications for fibrinolytic use in STEMI including : History of chronic severe poorly controlled hypertension, Significant hypertension on presentation (systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg, Traumatic or prolonged (>10 minutes) cardiopulmonary resuscitation (CPR) or major surgery less than 3 weeks previously, History of prior ischemic stroke not within the last 3 months, Dementia , Recent (within 2-4 weeks) internal bleeding, Non compressible vascular punctures , Pregnancy, Active peptic ulcer , Current use of an anticoagulant (eg, warfarin sodium) that has produced an elevated international normalized ratio (INR) higher than 1.7 or a prothrombin time (PT) longer than 15 seconds.

Adverse effects of Thrombolytic therapy

Adverse effects of any fibrinolytic agents are almost similar, which include, but are not limited to, bleeding, hypotension, allergic reactions, angioedema, and reperfusion arrhythmias (when used in acute MI). Among all fibrinolytic agents, streptokinase is the most antigenic; thus, it is most frequently complicated by allergic reactions and hypotension .

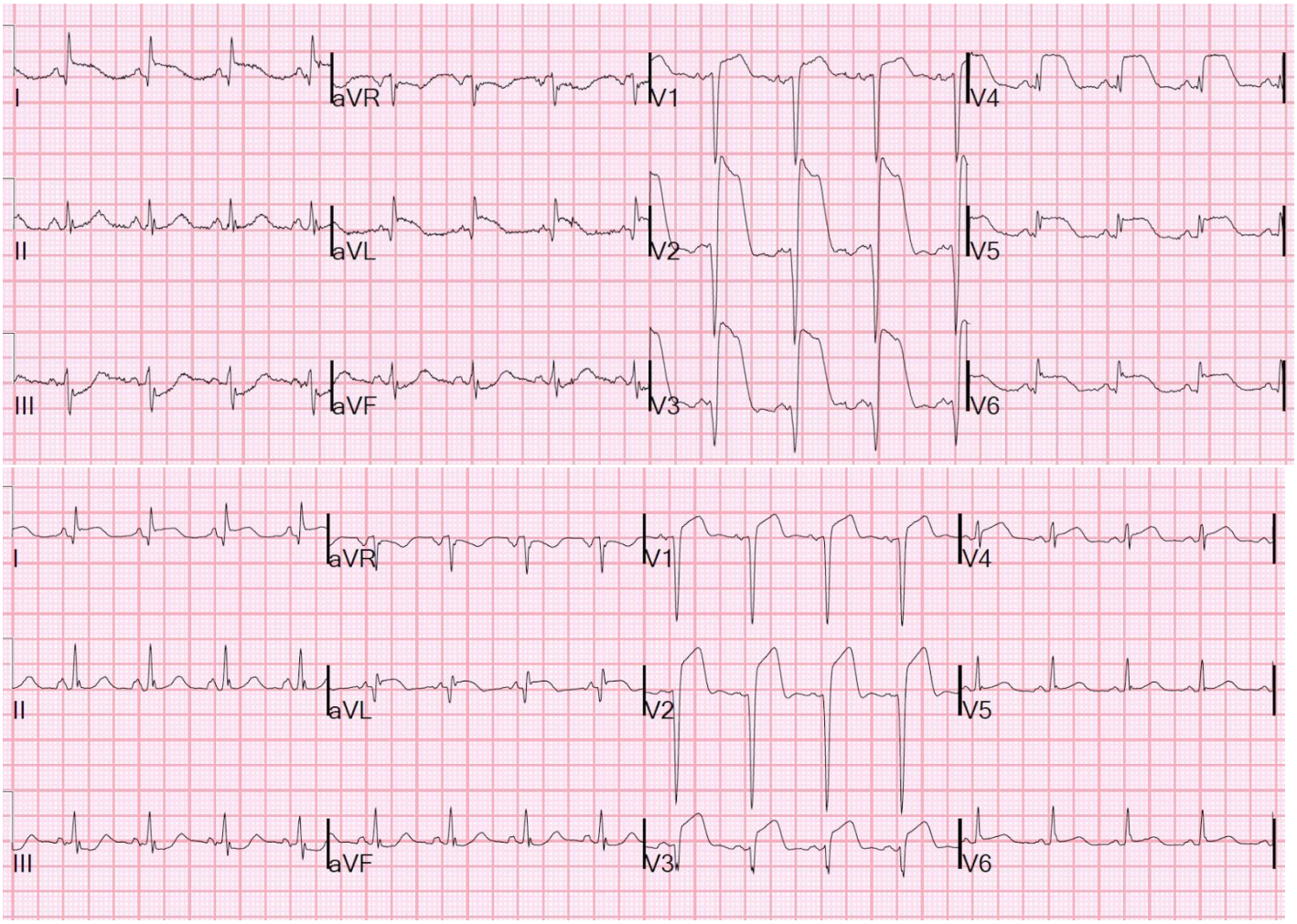
Bleeding is the most frequent complication of thrombolytic therapy and can occur in puncture sites or spontaneously anywhere inside the body. Intracranial hemorrhage or hemorrhagic stroke is the greatest concern. Risk factors associated with hemorrhagic complications include elderly patients, uncontrolled hypertension, recent stroke or surgery, presence of bleeding diathesis, and concurrent use of anticoagulants. Overdose most often occurs when administered in a non-body-weight adjusted manner and can cause severe hemorrhagic complications. [12]

Response to thrombolytics

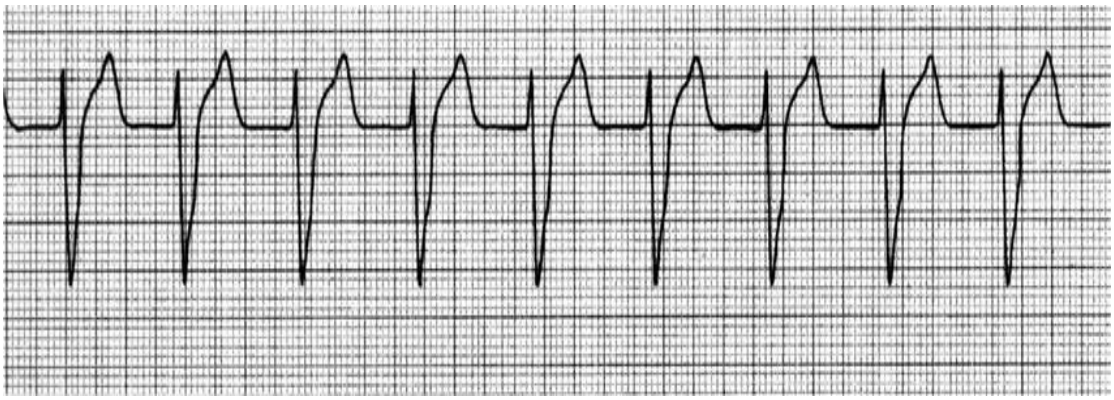
The successful rate of thrombolytics is highly variable . in one study Among 83 patients with STEMI 50.6% were males and 49.4% were females with the age group range of 30-83 years. Fifty nine patients (71.08%) with STEMI underwent thrombolysis within 12 hours of onset of chest pain while 24 patients (28.92%), underwent thrombolysis after 12 hours of onset of chest pain. Out of the 59 patients who received thrombolytic therapy before 12 hours, 43 (72.88%)completely resolved, while those who received thrombolytic therapy after 12 hours none of them completely resolved as per ECG findings. [13]

Successful clinical reperfusion (SCR) is defined as the presence of at least two of the following criteria at 2 hours after thrombolytic treatment: (1) significant relief of pain (a 5-point reduction on a 1 to 10 subjective scale), (2) ≥50% reduction of sum of ST segment elevation, and (3) abrupt initial increase of creatine kinase levels (more than twofold over the upper-normal or baseline elevated values).

ECG because it is simple, easily done, not invasive and has a well-established role in evaluating the effect of thrombolytic therapy In patients who presented with ST- elevation Acute Myocardial Infarction (AM I) by ECG changes based on the criteria of reduction in the ST segment. other changes in the ECG, with respect to the ST Reduction criterion as rapid appearance of Q wave , rapid appearance of T inversion, and appearance of accelerated idioventricular rhythm (AIVR) by ECG or monitor. Persistence or disappearance of reciprocal changes.



There is greater than 50% resolution of ST elevation (all but diagnostic of successful reperfusion) and Terminal T-wave inversion (also highly suggestive of successful reperfusion)



Accelerated Idioventricular Rhythm (AIVR) Overview

- Regular rhythm
- Rate typically 50-120 bpm
- Three or more ventricular complexes; QRS duration > 120ms

Aim of study

- To assess the response of STEMI patients admitted to baqubah teaching Hospital to the thrombolytic therapy .

- To look for short-term outcome of patients receiving thrombolytic therapy.

Patients and method

At Baqubah teaching Hospital , Diyala , Iraq , we analyzed in a cross sectional study, patients with STEMI who were receiving thrombolytic therapy at the time of hospital enrollment who had been admitted in the cardiac care unit . data analyzed using frequency , percentage.

We considered STEMI , if ST elevation at least 0.1mv in two or more limb leads , or at least 0.2mv in two or more contagious precordial leads.

The success of thrombolytic treatment considered if patient get his symptoms improvement , reduction in amplitude of ST elevation to 50% of initial amplitude , or development of reperfusion arrhythmia .

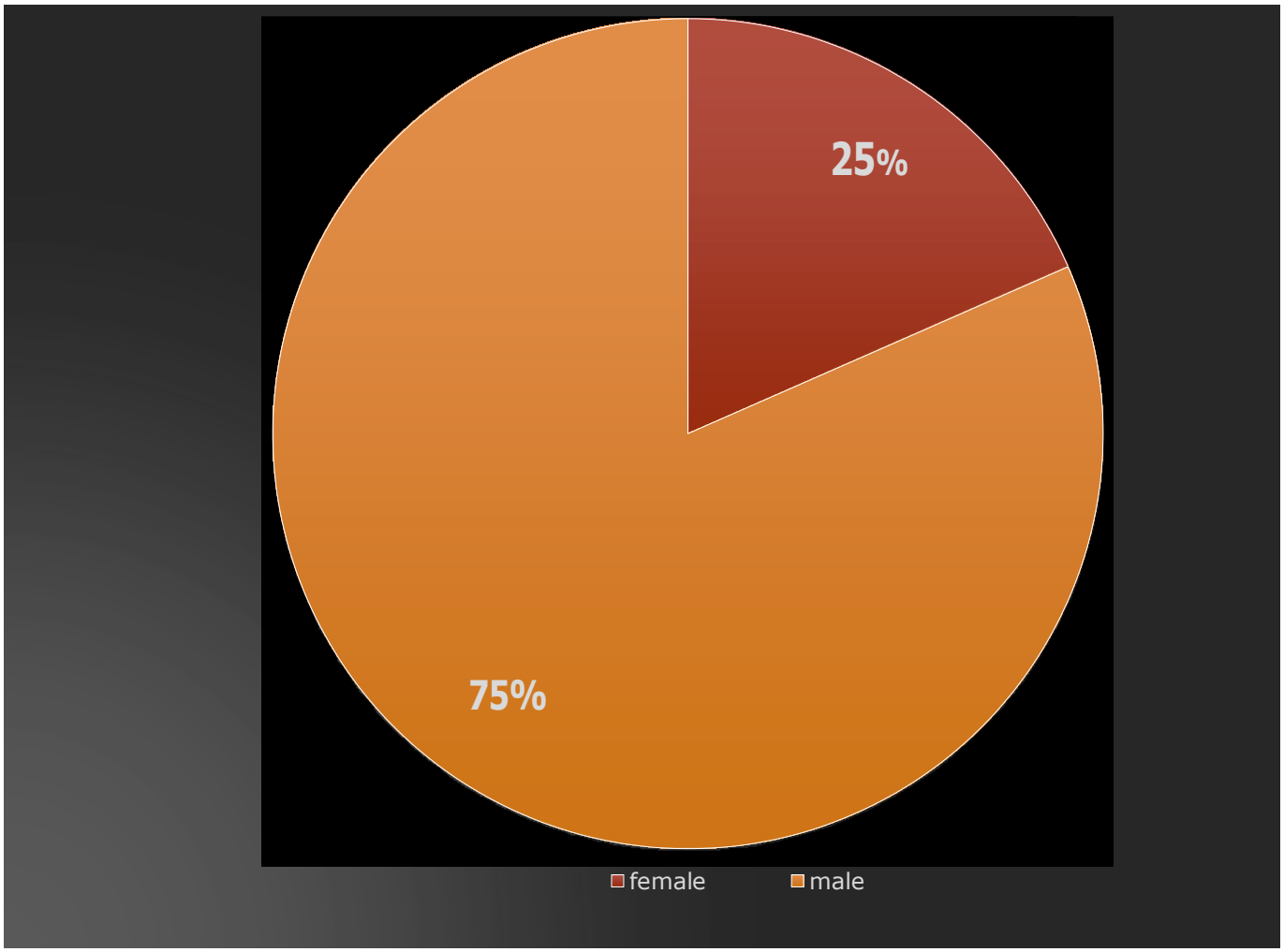
This interventional study was conducted from 6th December 2022 till 28rd March 2023, Data was collected through established questionnaire that included patient age, sex, weight, Hight , occupation , smoking or alcohol consumption , diagnosed chronic illness , previous COVID-19 infection, main symptoms at presentation , time from symptom onset till hospital admission , time from symptom onset till receiving thrombolytics ,previous use of antiplatelet, anticoagulants and thrombolytics . The questionnaire also focused on localization of ischemic area on ECG, amplitude of ST elevation , lead with maximum ST elevation , residual LV function based on EF by ECHO study, any mechanical complication of MI , and the short outcome of patients .

Samples involved 52 patients of different age and both sex , regardless their past medical history and compliance with treatment , all of them received thrombolytic agent ,which is alteplase of 100mg slow infusion over 2 hours on continuous ECG monitoring within first 12 hours of their symptoms onset.

The samples also followed throughout their hospital stay looking for short-term outcome of alteplase on patient's health.

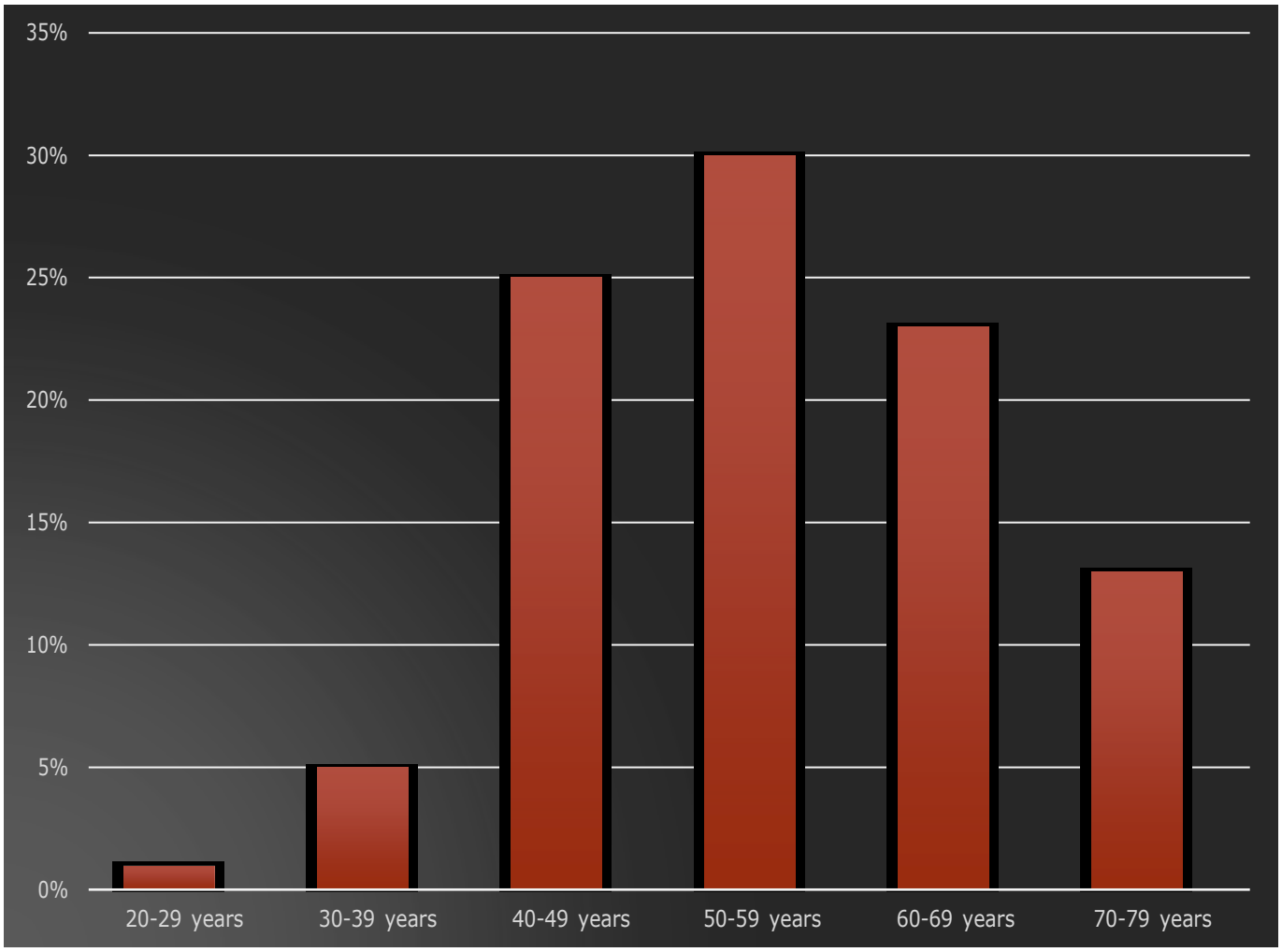
Results

Figure (1) :Pie chart demonstrate frequency of gender in the samples involved in the study .



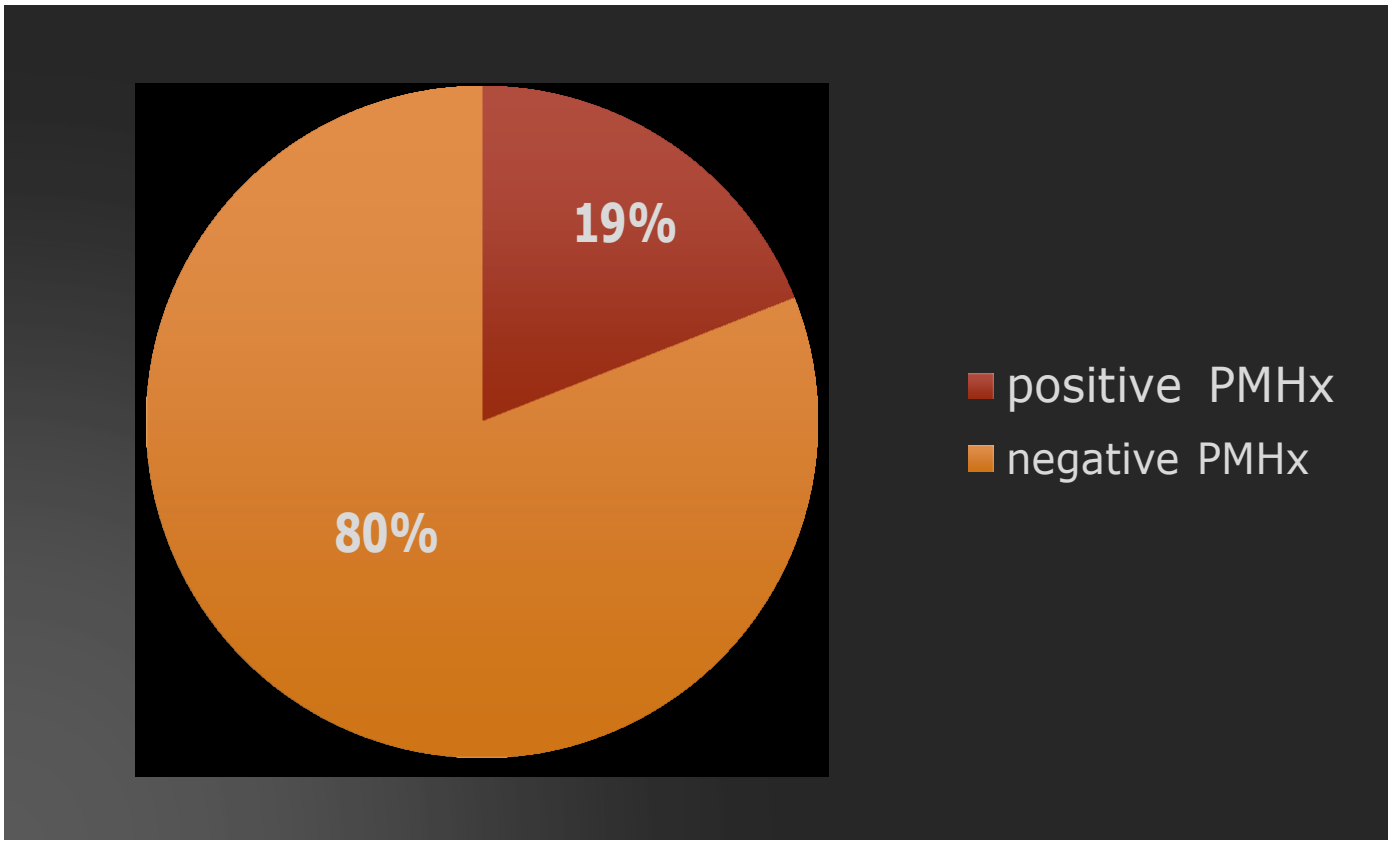
From total number of 52 patients were taken , 13(25 %) were female and 39 (75 %) were male , so male gender was the predominant in this study.

Figure (2) :Bar chart demonstrate age groups of patients involved in the study .



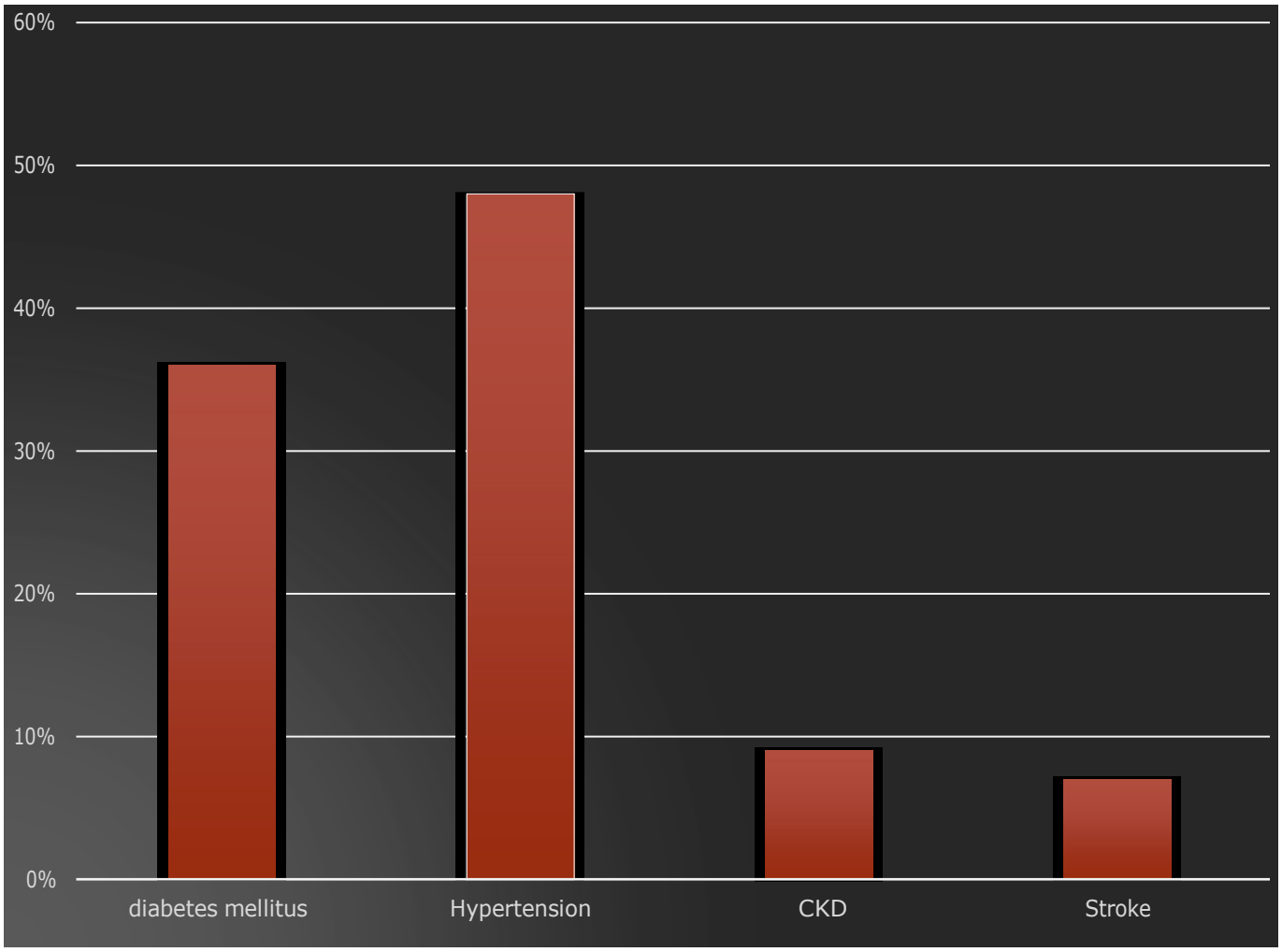
In this study , total number of patient were 52 . regarding age group distribution , 1(1%) patient was in age group between 20-29 years, 3(5%) patient was in age group between 30-39 years, 13 (25%) patients were in age group between 40-49 years, 16(30%) patients were in age group between 50-59 years, 12 (23%) patients were in age group between 60-69 years, 7 (13%) patient were in age group between 70-79 years, , so 50-59 years age group was most predominant age group in this study .

Figure(3):Pie chart shows frequency of patients who involved in this study who had positive past medical history .



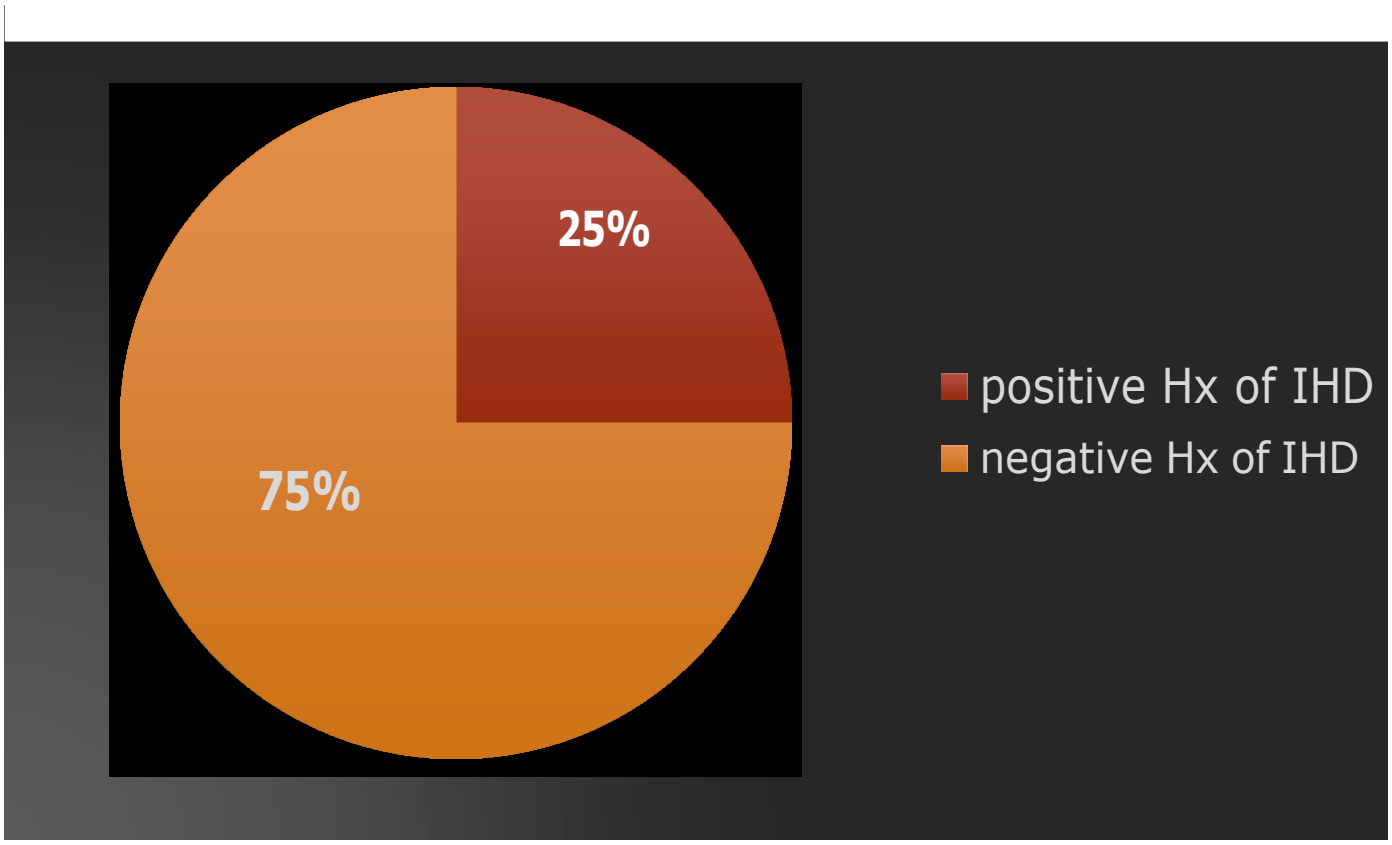
In this study , from whole of 52 patients encountered , 10 (20%) of them had negative past medical history , while 42 (80%) of them had positive medical history of hypertension , stroke , diabetes mellitus , chronic kidney disease.

Figure(4):Bar chart demonstrate frequency of chronic disease in patients involved in the study .



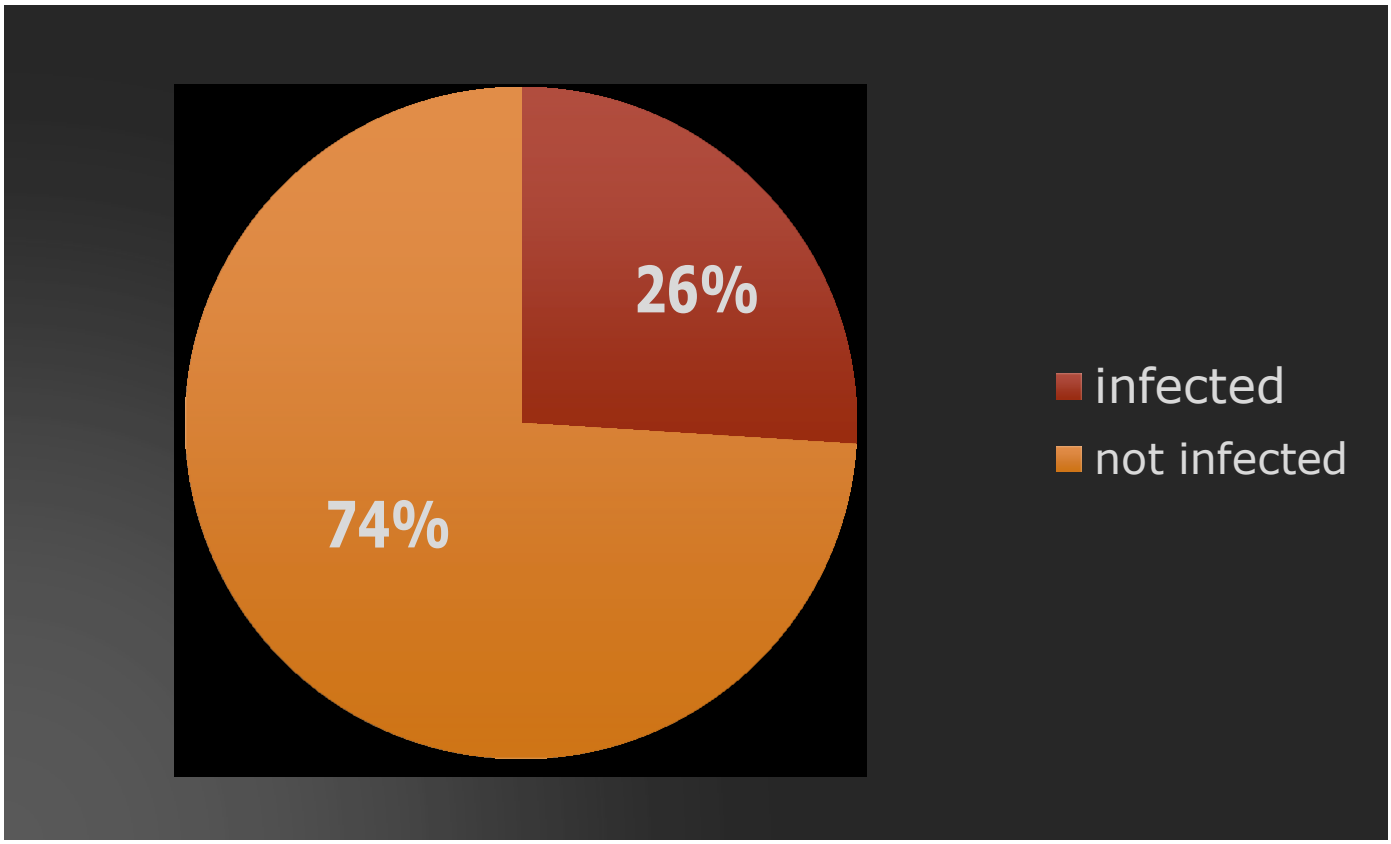
In this study , total number of patient were 52 . regarding chronic disease distribution , 25 (48%) of patients were with Hypertension , 19 (36%) of them with diabetes mellitus , 5 (9%) with chronic kidney disease ,and 4 (7%) with cerebrovascular disease.

Figure(5): Pie chart shows frequency of patients who involved in this study who had previous history of ischemic heart disease .



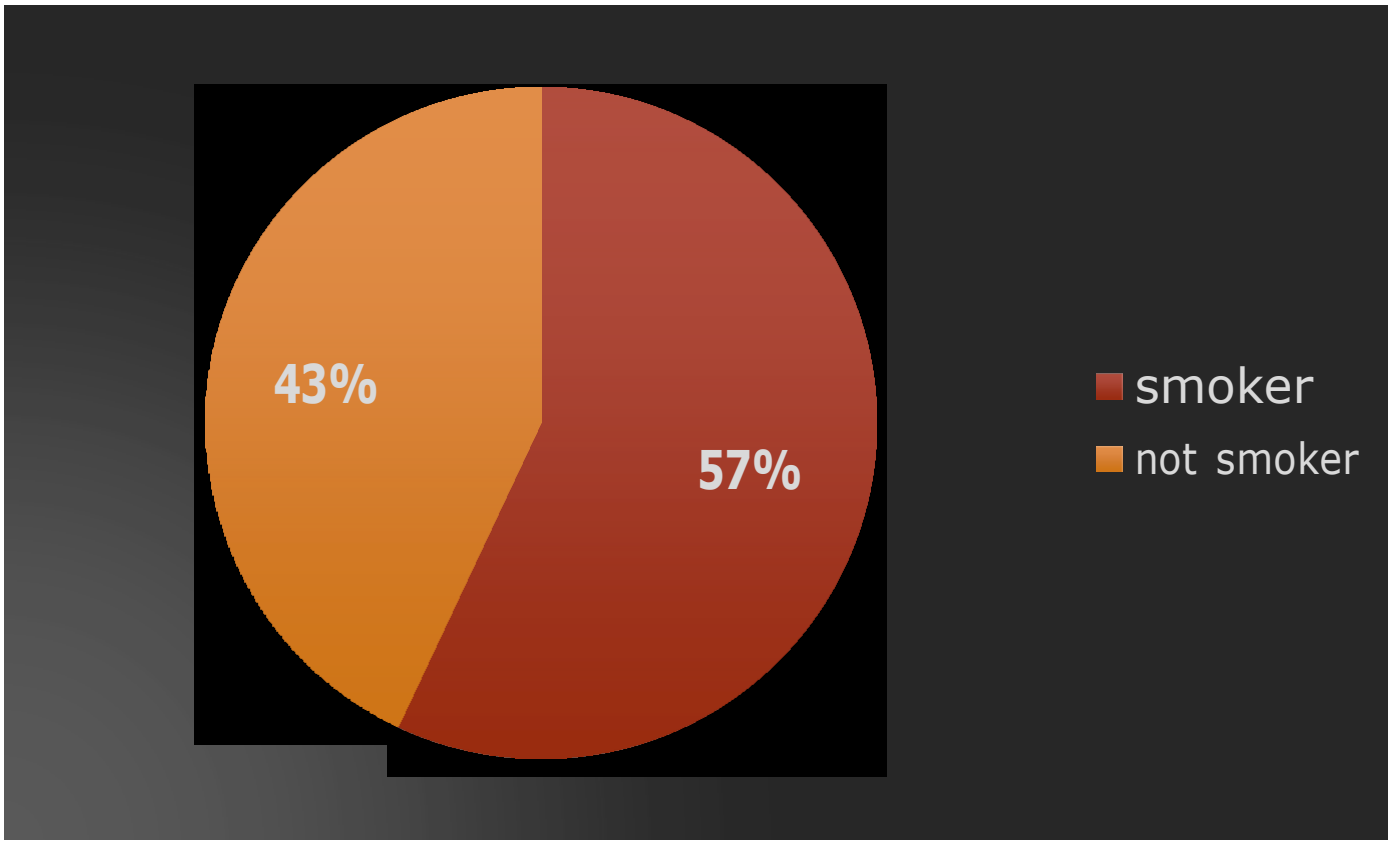
In this study , from whole of 52 patients encountered , 13 (25%) of them had previous history of IHD , while 39 (75%) of them had no history of similar illness.

Figure(6): Pie chart shows frequency of patients who involved in this study had COVID-19 infection .



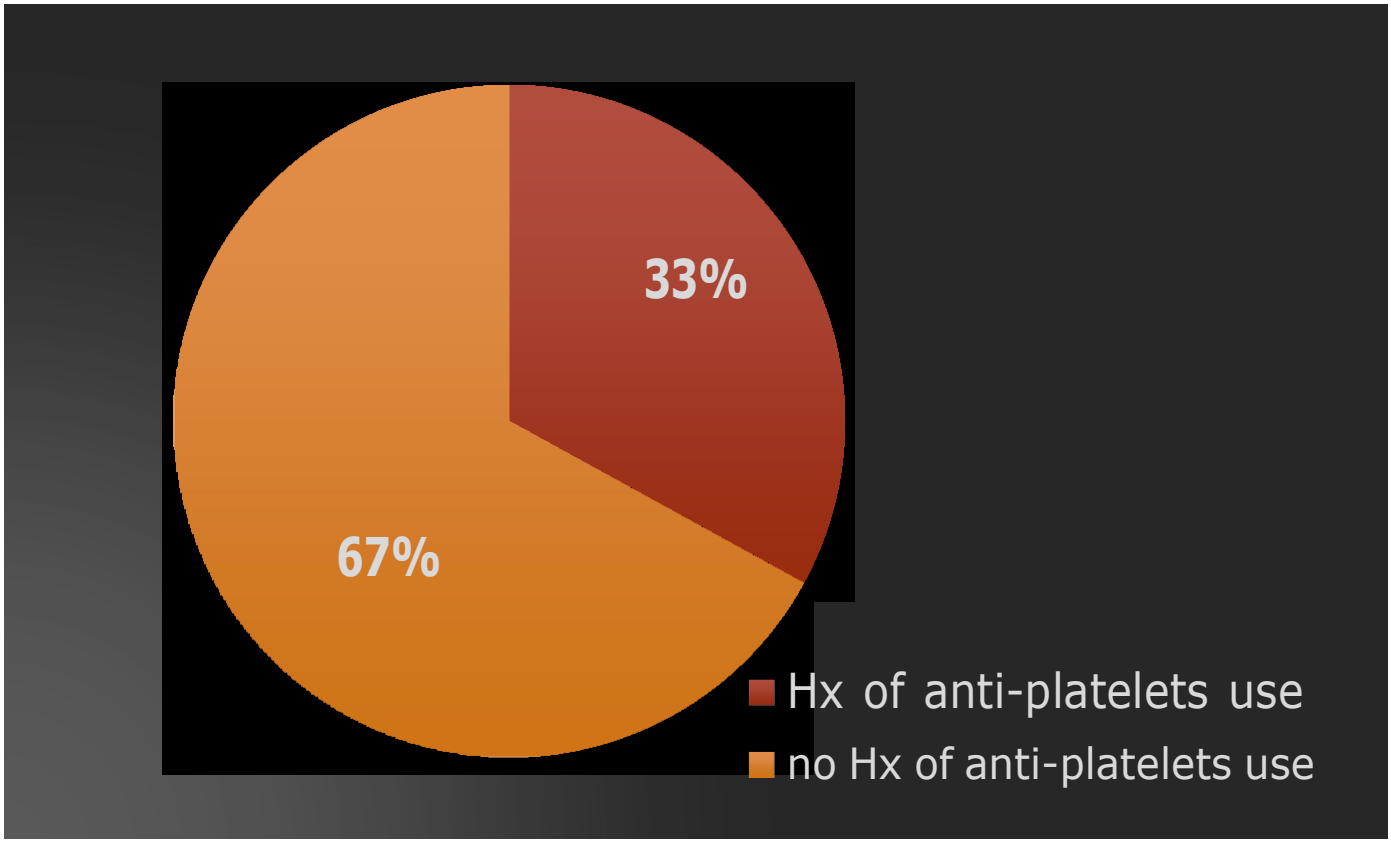
In this study , from whole of 52 patients encountered , 14 (26%) of them were infected by COVID-19 in the past , while 38 (74%) of them had no infection recorded.

Figure(7): Pie chart shows frequency of patients who involved in this study were smoker .



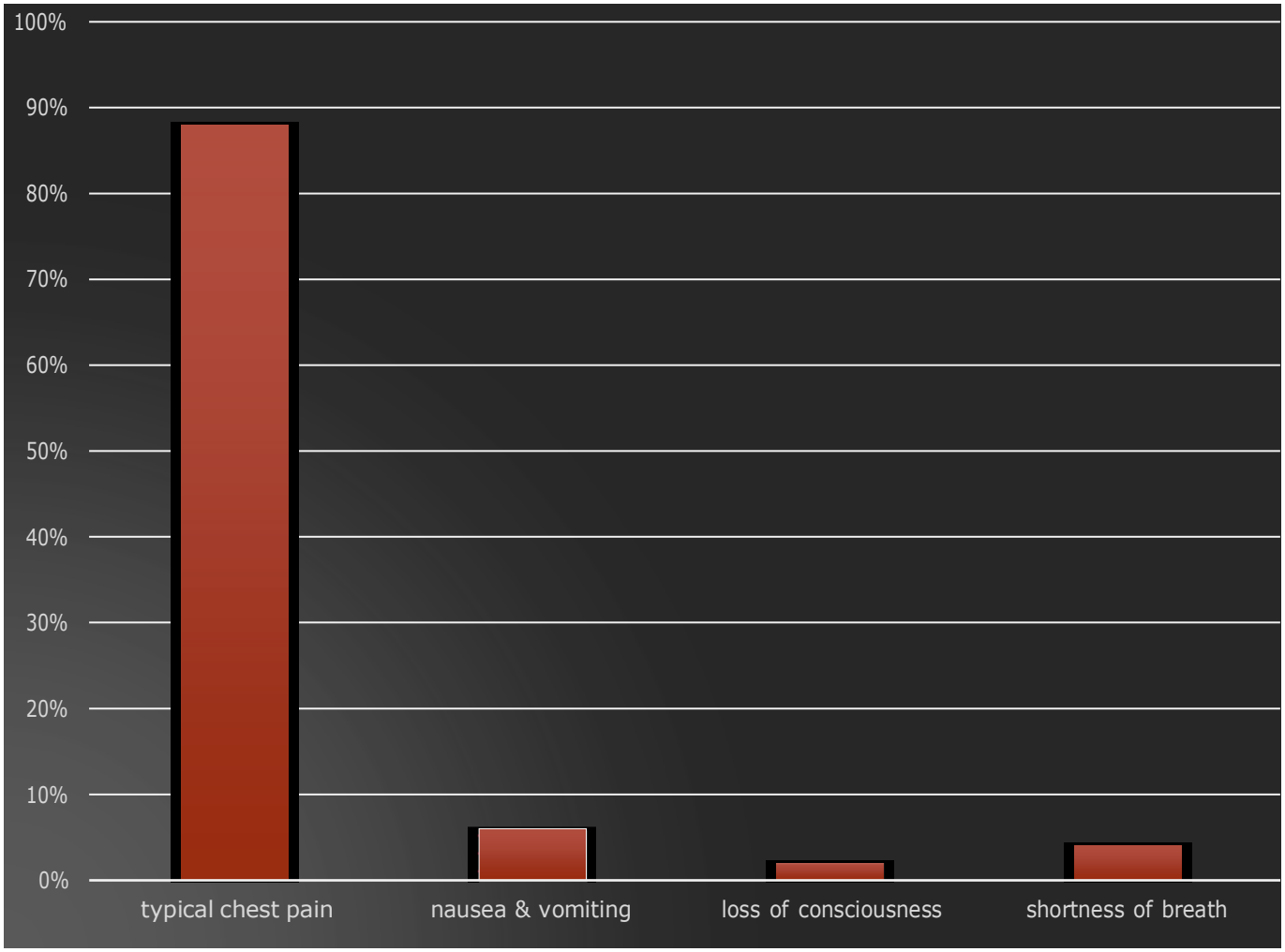
In this study, from whole of 52 patients encountered , 30 (57%) of them were smoker , while 22 (43%) of them were not smoker .

Figure (8): Pie chart shows frequency of patients who involved in this study who had positive history of anti-platelets drug usage .



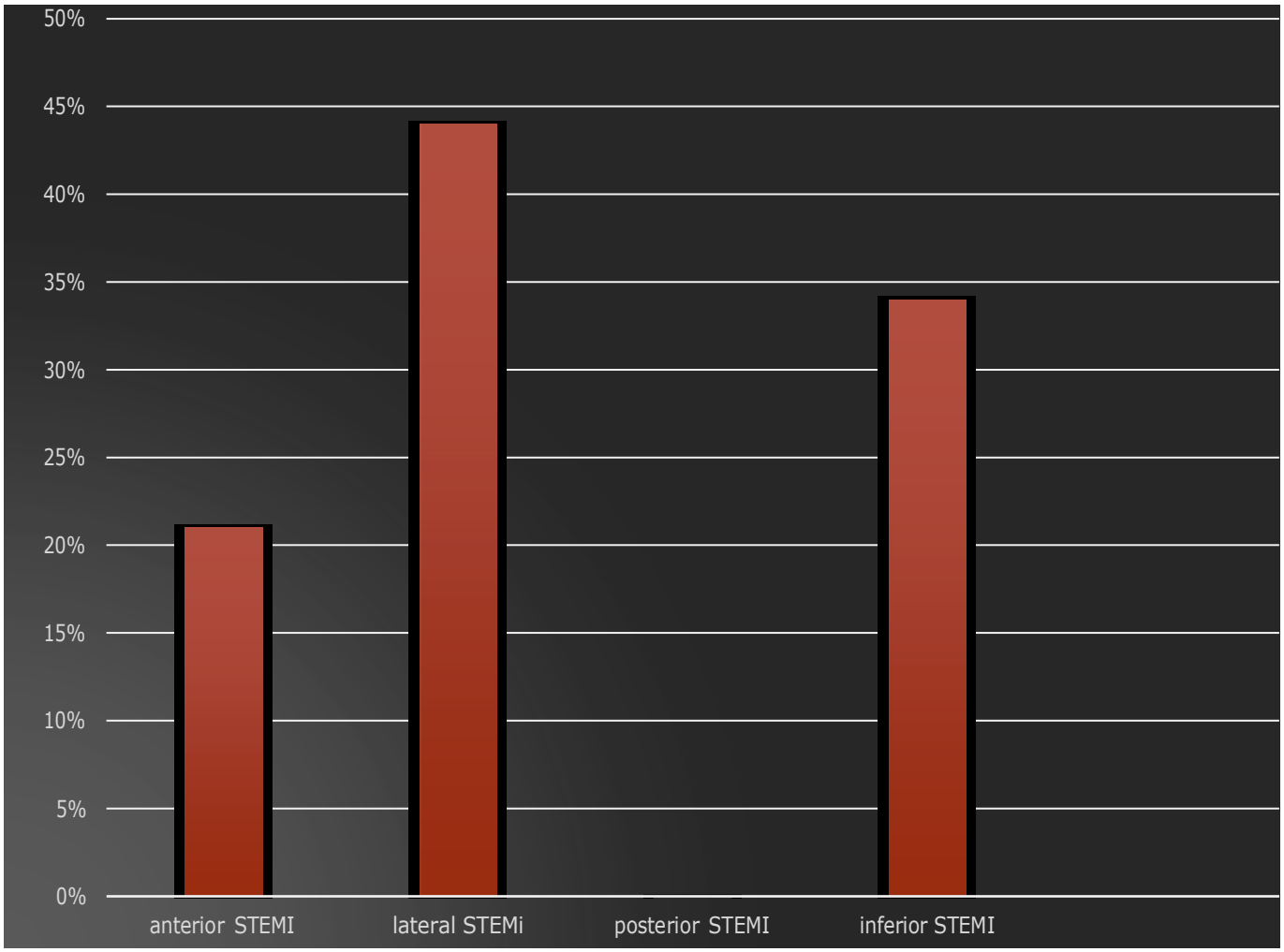
In this study , from whole of 52 patients encountered , 17(32%) of them Were on anti-platelet drugs , while 35(67%) of them had negative history of anti-ischemic drug usage.

Figure (9) :Bar chart shows frequency of different presentations in patients involved in this study .



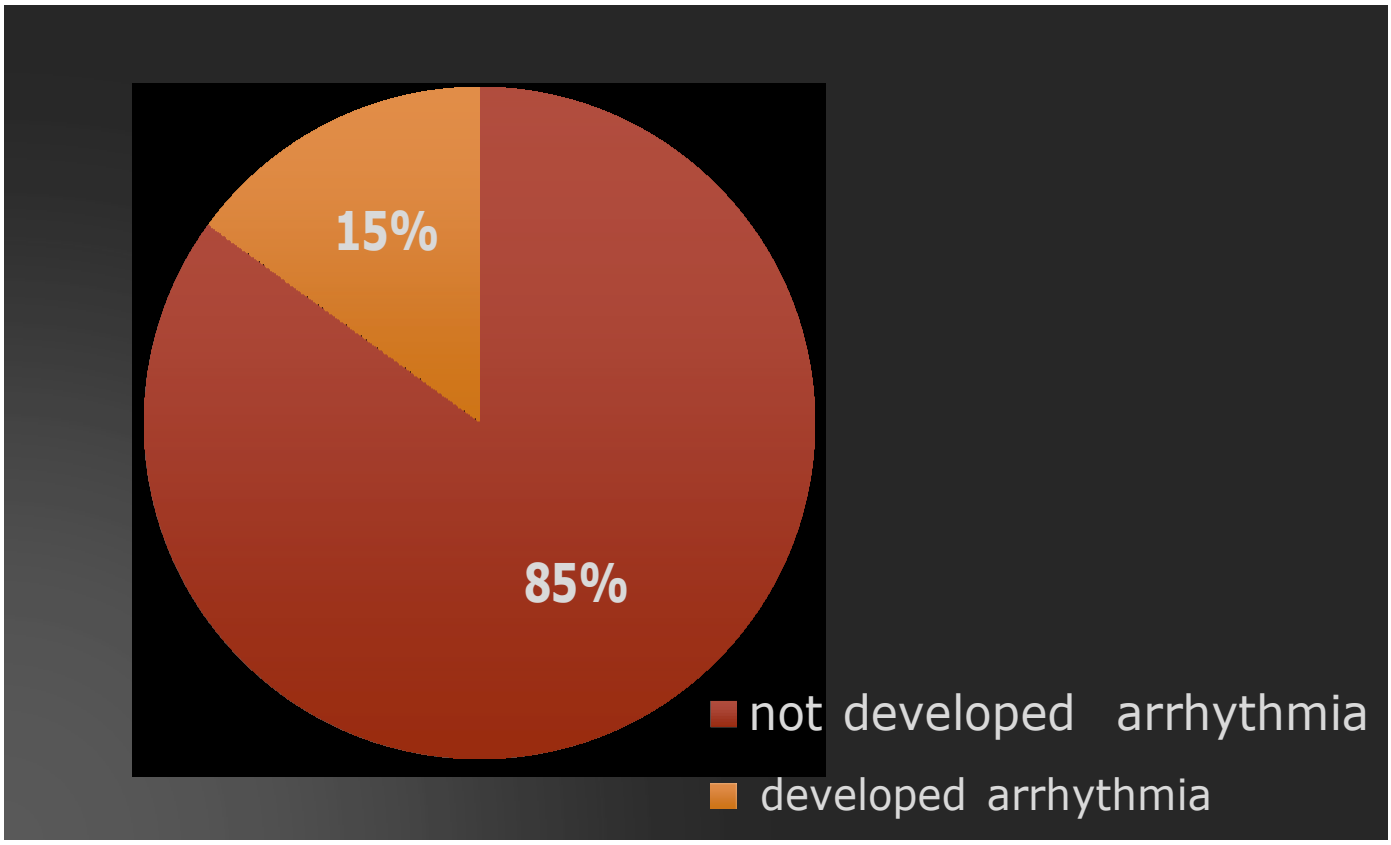
In this study , only 6 (12%) from a total of 52 patients presented with atypical presentation . 1(2%) in form of loss of consciousness , 3(6%)patients in form of nausea and vomiting , 2(4%) patients in form of shortness of breath , while 46(88%) of them had typical presentation of central chest pain . All patients with atypical symptoms respond to thrombolytics.

Figure (10):Bar chart demonstrate the most frequent STEMI based on localization of ischemic area on ECG that encountered in this study.



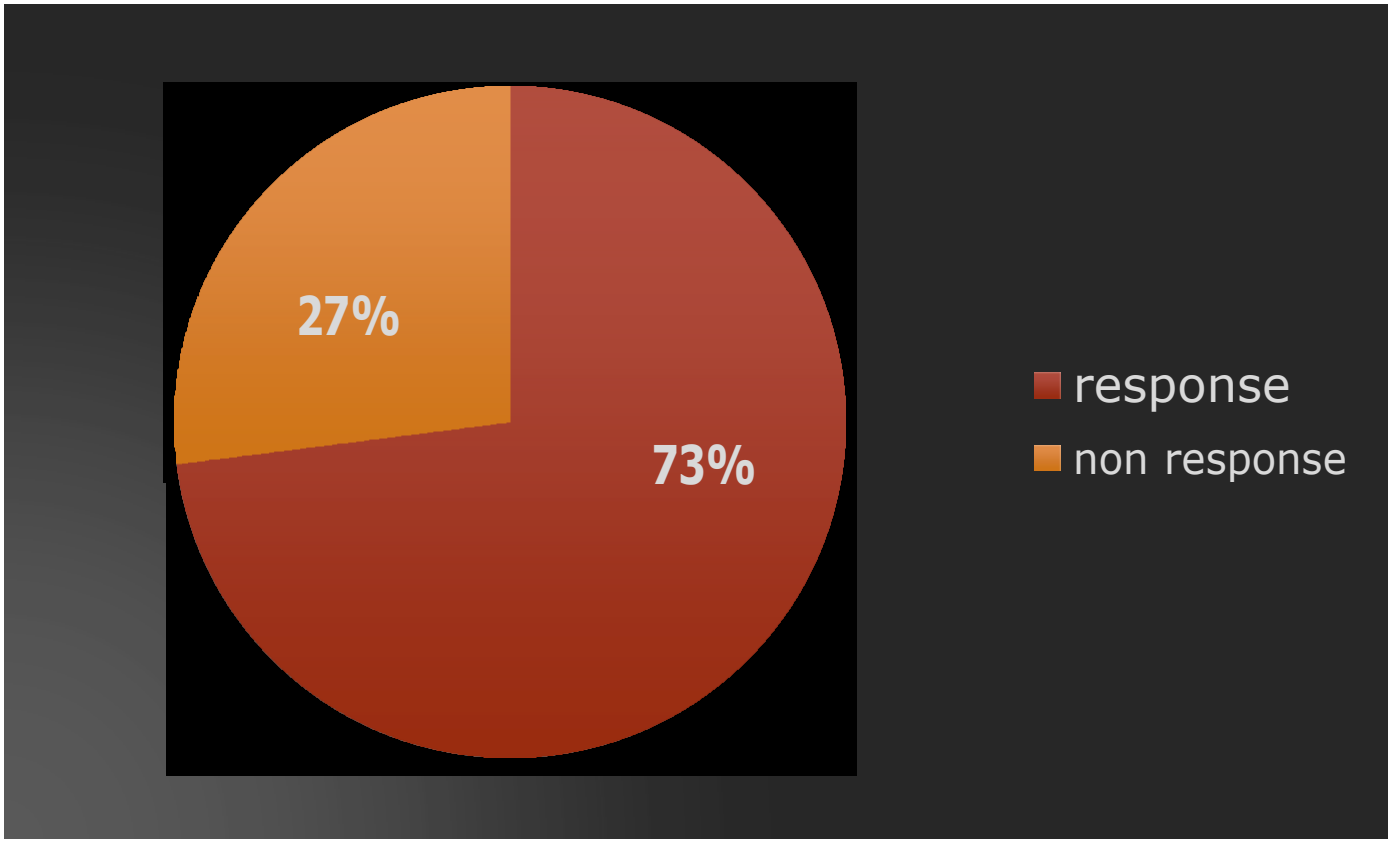
In this study , of the total samples of 52 patients , the lateral STEMI was the most frequent with 23(44%) patients presented with , followed by inferior STEMI with 18(34%) patients, anterior STEMI with 11(21%) patients, while no patient was recorded with posterior STEMI.

Figure (11): Pie chart shows the frequency of patients who got successful outcome from thrombolytic therapy who developed reperfusion arrhythmia.



In this study, only 6 (15%) from total of 38 of patients who got successful outcome from thrombolytic therapy developed reperfusion arrhythmia, while no one of other 32 (85%) developed reperfusion arrhythmia.

Figure(12): Pie chart shows the responsiveness to thrombolytic therapy



In this study , from whole of 52 patients received thrombolytic agent ,which is alteplase , 38 (73%) of them got full response , while 14(27%) of patient failed to get the response.

Table(1): Demonstrate the responsiveness to the thrombolytic therapy in each age groups of patients involved in the study .

Age group	Respond	Not respond	Total
20-29	0	1(1%)	1(2%)
30-39	2(66%)	1(33%)	3 (6%)
40-49	10(76%)	3(23%)	13(25%)
50-59	11(68%)	5(31%)	16(31%)
60-69	10(83%)	2(17%)	12(23%)
70-79	5(71%)	2(29%)	7(13%)
	38	14	52(100%)

In this study , from whole of 52 patients received thrombolytic agent ,which is alteplase , in age group between 20-29 years , only 1(2%)patient was involved and didn't respond to thrombolytics . in age group between 30-39 years , from 3(6%) patients were involved , 2(66%) of them responded and 1(33%) non-responder . in age group between 40-49 years , from 13(25%) patients were involved , 10(76%) of them responded and 3(23%)non-responder . in age group between 50-59 years, from 16(31%) patients were involved , 11(68%) of them responded and 5(31%) non-responder. in age group between 60-69 years , from 12(23%) patients were involved , 10(83%) of them responded and 2(17%) non-responder. in age group between 70-79 years , from 7(13%) patients were involved , 5(71%) of them responded and 2(29%) non-responder.

Table(2): Demonstrate the relationship between responsiveness to the thrombolytic therapy and gender of patients involved in the study .

Gender 1	Respond	Not respond	Total
Male	28(71%)	11 (29%)	39(75%)
Female	10 (76%)	3 (23%)	13(25%)
	38	14	52

In this study , from whole of 39(75%) male patients , who received thrombolytic agent, 28 (71%) of them responded and 11(29%) were not responder. from whole of 13 (25%)female patients, 10 (76%) of them responded and 3 (23%) were not responder.

Table(3): Demonstrate the relationship between responsiveness to the thrombolytic therapy and past medical history of patients involved in the study .

Past Medical history	Respond	Not respond	Total
Positive PMHx	31(71%)	11 (29%)	42 (80%)
Negative PMHx	7(76%)	3 (24%)	10 (20%)
	38	14	52

In this study , from whole of 42 patients with positive past medical history encountered , 31(71%) of them responded to thrombolytic therapy , while 11 (29%) of them were non- responder. from whole of 10 patients with negative past medical history encountered , 7(76%) of them responded to thrombolytic therapy , while 3 (24%) of them were non- responder.

Table(4): Demonstrate the relationship between responsiveness to the thrombolytic therapy and each chronic disease in patients involved in the study .

Diseased patients	Respond	Not respond	Total
hypertensive	19 (76%)	6 (24%)	25(48%)
Diabetic	14 (73%)	5 (26%)	19(37%)
Stroke	3 (75%)	1 (25%)	4(7%)
Chronic kidney disease	4 (80%)	1 (20%)	5(9%)
Ischemic heart disease	9 (69%)	4 (31%)	13(25%)

In this study , from whole of 25(48%) hypertensive patients received thrombolytic agent, 19 (76%)of them responded and 6 (24%) were not responder. from whole of 19(37%) diabetic patients received thrombolytic agent, 14 (73%)of them responded and 5 (26%)were not responder. from whole of 4(7%) patients with stroke received thrombolytic agent, 3 (75%)of them responded and 1 (25%) were not responder. from whole of 5(9%) CKD patients received thrombolytic agent, 4 (80%)of them responded and 1 (20%) were not responder. from whole of 13(25%) patients with ischemic heart disease received thrombolytic agent, 9 (69%) of them responded and 4 (31%) were not responder.

Table(5): Demonstrate the relationship between responsiveness to the thrombolytic therapy and history of COVID-19 infection in patients involved in the study .

Hx of COVID-19 infection	Respond	Not respond	Total
Infected	10 (71%)	4 (29%)	14(27%)
Not infected	28 (73%)	10 (26%)	38(73%)
	38	14	52

In this study , from whole of 14(27%) patients infected with COVID-19 in the past , who received thrombolytic agent, 10 (71%) of them responded and 4 (29%) were not responder. from whole of 38(73%) patients with negative history of COVID-19 infection , 28 (73%) of them responded and 10 (26%) were not responder.

Table(6): Demonstrate the relationship between responsiveness to the thrombolytic therapy and history of smoking in patients involved in the study.

Hx of smoking	Respond	Not respond	Total
Smoker	20(66%)	10(33%)	30(58%)
Non smoker	17(77%)	5(23%)	22(42%)
	37	15	52

In this study , from whole of 30 (58%)patients who were smoker in the past , who received thrombolytic agent, 20 (66%) of them responded and 10 (33%) were not responder. from whole of 22 (42%)patients with negative history of smoking , 17 (77%) of them responded and 5 (23%) were not responder.

Table(7): Demonstrate the relationship between responsiveness to the thrombolytic therapy and history of anti-platelets usage in patients involved in the study.

Hx of anti-platelets usage	Respond	Not respond	Total
Positive history	15(88%)	2(12%)	17(32%)
Negative history	23(65%)	12(34%)	35(67%)
	38	14	52

In this study , from whole of 17 (32%)patients who have positive history of anti-platelets usage , who received thrombolytic agent, 15 (88%) of them responded and 2 (12%) were not responder. from whole of 35(67%) patients with negative history of anti-platelets usage , 23 (65%) of them responded and 12 (34%) were not responder.

Table(8): Demonstrate the relationship between responsiveness to the thrombolytic therapy and types of STEMI in patients involved in the study.

Types of STEMI	Respond	Not respond	Total
Anterior STEMI	9 (82%)	2(18%)	11(21%)
lateral STEMI	16(70%)	7(30%)	23(44%)
Inferior STEMI	13 (72%)	5 (28%)	18(34%)
	38	14	52

In this study , from whole of 23 patients who have lateral STEMI , who received thrombolytic agent, 16(70%) of them responded and 7(30%) were not responder. from whole of 18 patients with inferior STEMI , 13(72%) of them responded and 5(28%) were not responder. from whole of 11 patients with anterior STEMI , 9(82%) of them responded and 2(18%) were not responder. No posterior STEMI cases encountered .

Table(9): Demonstrate the relationship between responsiveness to the thrombolytic therapy and duration from onset of symptoms till initiating thrombolytics in patients involved in the study.

Duration	Respond	Not respond	Total
<1hr	4(11%)	1(7%)	5
1-2hrs	8(21%)	3(21%)	11
2-3hrs	9(24%)	4(29%)	13
>3hrs	17(45%)	6(43%)	23
	38	14	52

In this study , 17(45%) from whole of 38 patients who got successful outcome from thrombolytic therapy presented after 3 hours from symptoms onset , while 9(24%) of these patients presented between 2-3 hours , 8(21%) patients presented within1-2hours , and only 4(11%) patients presented within first 60 minutes .

6(43%) from whole of 14 patients who failed to respond for thrombolytic therapy presented after 3 hours from symptoms onset , while 4(29%)of these patients presented between 2-3 hours , 3(21%) patients presented within1-2hours , and only 1(7%) patients presented within first 60 minutes .

Table(10) :Demonstrate the short term outcomes of thrombolytic therapy in patients involved in the study.

Short-term outcome	cases	Type of outcome
Side effect of thrombolytics	1(1%)	GIT bleeding
VT/VF after 24hrs	3(6%)	2 VT , 1VF
Death	1(1%)	Asystole
Discharged	48(92%)	Without complication

In this study, only 4 (7%) from total of 52 of patients had worse outcome , 1 case which had history of peptic ulcer developed GIT bleeding controlled medically without surgical intervention , 2 cases developed ventricular tachycardia , 1 case developed ventricular fibrillation , 1 case die due to cardiac asystole , no mechanical complication encountered , while 48(92%) patient discharged without complication at hospital .

Discussion

Myocardial infarction (MI) is a leading cause of morbidity and mortality in the worldwide. The estimated annual incidence of MI in the United States is approximately 550,000 new attacks and 200,000 recurrent attacks. [(1)] Fibrinolytic therapy is a proven treatment for the management of AMI. Fibrinolytic therapy can reduce the relative risk of in-hospital death by up to 50% when administered within the first hour of the onset of symptoms of STEMI, and much of this benefit is maintained for at least 10 years.

The successful rate of thrombolytics is highly variable , affected by many factors , including age of the patient , comorbidities , and duration since onset of symptoms. Successful clinical reperfusion (SCR) is defined as the presence of at least two of the following criteria at 2 hours after thrombolytic treatment: (1) significant relief of pain (a 5-point reduction on a 1 to 10 subjective scale), (2) ≥50% reduction of sum of ST segment elevation, and (3) abrupt initial increase of creatine kinase levels (more than twofold over the upper-normal or baseline elevated values).

In this study , from whole of 52 patients received thrombolytic agent, 38 (73%) of them got full response , while 14(27%) of patient failed to get the response. On other study, Results of thrombolysis were evaluated in 156 consecutive acute myocardial infarction patients admitted to the Intensive Cardiac Care Unit during the period 1 July 1995 to 1 July 1996. The study population consisted of 121 males and 35 females, age range 32–89 years (mean 64.47 ± 11.79 SD). Thrombolysis was determined to have been successful in 88 patients (56.4%), failed in 48 patients (30.8%) and equivocal in 20 patients (12.8%).[(20)]

In this study , from whole of 52 patients received thrombolytic agent , data demonstrate the increasing in the STEMI occurrence with age progression with peak age group between 50-59 years , while the peak response to thrombolytics was in age group between 60-69 years . In other study , 62 patients aged < 35 years (group 1) were compared with 58 aged > 55 years (group 2) who presented with acute myocardial infarction , both treated with thrombolytics . similar patency rates of the infarct vessel (74 vs 73%) compared with those of group 2.[(28)]

Regarding the age **,** from total number of 52 patients were taken , 13(25%) were female and 39 (75 %) were male , so male sex was the predominant in this study. in other study, evaluated in 156 consecutive acute myocardial infarction patients , 121(78%)males and 35(22%) females . so male sex is risk factor for STEMI. [21]

from whole of 39(75%) male patients , who received thrombolytic agent, 28 (71%) of them responded and 11(29%) were not responder. from whole of 13 (25%)female patients, 10 (76%) of them responded and 3 (23%) were not responder. in other study , A total of 348 women were compared with 1,271 men were involved , All patients received recombinant tissue-type plasminogen activator, urokinase or a combination of both agents. Rates of acute and predischarge infarct-related artery patency and global and regional left ventricular function were similar in the two groups. The extent to which gender itself explains observed differences in outcome and use of diagnostic procedures remains unclear because confounding factors have not been specified.[29]

In this study , from whole of 52 patients encountered , 10 (20%) of them had negative past medical history , while 42 (80%) of them had positive medical history of hypertension , stroke , diabetes mellitus , chronic kidney disease. Hypertension was most encountered in 48%. That explain the prominent linkage role of comorbidities on the incidence of ischemic heart disease. One study done on 302 Hanoi residents hospitalized with a first AMI at the largest tertiary care medical center in Hanoi in 2010, The average age of study patients was 66 years and one third were women. The proportions of patients with none, any 1, and ≥ 2 CVD comorbidities were 34%, 42%, and 24%, respectively. Among the CVD comorbidities, hypertension was the most commonly reported (59%). There were decreasing trends in the proportion of patients who were treated with effective cardiac medications and coronary interventions as the number of CVD comorbidities increased.[16]

Regarding the response to thrombolytics in patients with chronic disease , from whole of 25(48%) hypertensive patients received thrombolytic agent, 19 (76%)of them responded and 6 (24%) were not responder. from whole of 19(37%) diabetic patients received thrombolytic agent, 14 (73%)of them responded and 5 (26%)were not responder. In other study , Among 83 patients with STEMI 50.6% were males and 49.4% were females with the age group range of 30-83 years. in non-diabetics out of 55, 37 (67.27%) completely resolved, 12 (21.82%) partially resolved and 6 (10.91%) failed to resolve. Among 61 hypertensive, 26 (42.62%) had complete resolution and in 22 who were non-hypertensive, 17 (77.27%)had complete resolution on ECG. Hyperlipidemia and site of infarction didn't have statistically significant effect on the resolution of ECG post thrombolysis in STEMI patients.[35]

In this study , from whole of 52 patients encountered , 14 (26%) of them were infected by COVID-19 in the past , while 38 (74%) of them had no infection recorded. This explain the role of COVID-19 as risk factor for thrombosis and increase prevalence of ischemic heart disease . on one cross-sectional observational study on population included 1788 STEMI patients from 15 centers in Turkey. There was a 30.5% drop in STEMI admission during COVID-19 era in comparison to pre-COVID-19 era. The patients admitted to the medical centers during COVID-19 era had a longer symptom-to-first medical contact time [120 (75–240) vs. 100 (60–180) minutes, $p < 0.001$]. COVID-19 positive STEMI patients had higher thrombus grade and lower left ventricular ejection fraction compared to COVID-19 negative patients.(17)

Regarding relation between COVID-19 and response to thrombolytics , from whole of 14(27%) patients infected with COVID-19 in the past , who received thrombolytic agent, 10 (71%) of them responded and 4 (29%) were not responder. from whole of 38(73%) patients with negative history of COVID-19 infection , 28 (73%) of them responded and 10 (26%) were not responder. No data are available to develop uniform recommendations for reperfusion therapies in ST-segment elevation myocardial infarction (STEMI) during the coronavirus disease 2019 (COVID-19) pandemic.(31)

In this study, from whole of 52 patients encountered , 30 (57%) of them were smoker , while 22 (43%) of them were not smoker . this give an obvious risk of tobacco smoking on coronary artery disease. On a study included patients with incident STEMI registered in the Western Denmark Heart Registry from 2005 to 2015 (n=9914). Patients were divided into four age groups (30-49, 50-59, 60-69 and ⩾70 years) with the latter serving as reference. Smoking was the most prevalent modifiable risk factor in 30-49-year-old patients (74% vs. hypertension 15%, hyperlipidemia 10% and diabetes 7%). The smoking prevalence decreased with increasing age.(18)

Regarding smoking and response to thrombolytics , from whole of 30 (58%)patients who were smoker in the past , who received thrombolytic agent, 20 (66%) of them responded and 10 (33%) were not responder. from whole of 22 (42%)patients with negative history of smoking , 17 (77%) of them responded and 5 (23%) were not responder. in other study , we evaluated 1619 patients treated with TPA, urokinase, or both, of whom 878 (54%) were currently smoking. there were no differences between smokers and nonsmokers with regard to 90-minute patency (73% versus 74%). (30)

Regarding the most frequent symptoms at presentation , only 6 (12%) from a total of 52 patients presented with atypical presentation . 1(2%) in form of loss of consciousness , 3(6%)patients in form of nausea and vomiting , 2(4%) patients in form of shortness of breath , while 46(88%) of them had typical presentation of central chest pain , and all patients with atypical symptoms respond to thrombolytics successfully. In other study done on 94 consecutive patients (60 men and 34 women; mean age 68.5 +/- 11.5 years) with acute myocardial infarction (MI) were investigated retrospectively. An atypical MI was found in 30 patients, with a prevalence of 32% . It was most prevalent in women above 65 years old ($P < 0.05$). Abdominal pain, paroxysmal dyspnea, and pulmonary edema were the most frequent symptoms (33%, 17%, 13%, respectively).there was no obvious difference in responding to thrombolytics between typical and atypical cases. [19]

Regarding most frequent types of STEMI , from the total samples of 52 patients , the lateral STEMI was the most frequent with 23(44%) patients presented with , followed by inferior STEMI with 18(34%) patients, anterior STEMI with 11(21%) patients, while no patient was recorded with posterior STEMI. On a study done From 1987 through 2008, there were an estimated 4,845 incident hospitalized STEMIs in the four ARIC study communities among residents 35 to 74 years of age. Over the twenty-two year study period. Overall for all years combined, 37.2% of STEMIs were inferior; 32.8% anterior; 16.8% occurred in multiple infarct locations; and 13.2% were lateral.[20]

In this study , 17(45%) from whole of 38 patients who got successful outcome from thrombolytic therapy presented after 3 hours from symptoms onset , while 9(24%) of these patients presented between 2-3 hours , 8(21%) patients presented within1-2hours , and only 4(11%) patients presented within first 60 minutes .6(43%) from whole of 14 patients who failed to respond for thrombolytic therapy presented after 3 hours from symptoms onset , while 4(29%)of these patients presented between 2-3 hours , 3(21%) patients presented within1-2hours , and only 1(7%) patients presented within first 60 minutes . on a study analyzed nine trials of fibrinolytic therapy that had randomized more than 1000 patients each (n=58 600). They concluded that there was no marked discontinuity at 0 to 1 hours and only a gradual diminution of benefit with delay (30% reduction at 0 to 1 hours [SD, 9%]; 25% reduction at 2 to 3 hours [SD, 5%]; and 18% reduction at 4 to 6 hours [SD, 5%]). For each hour of delay in administering thrombolytic therapy, 1.6 additional lives were lost for every 1000 patients treated.[22]

In this study, only 6 (15%) from total of 38 of patients who got successful outcome from thrombolytic therapy developed reperfusion arrhythmia, while no one of other 32 (85%) developed reperfusion arrhythmia. On other study involved 97 patients , The age of patients ranged between 26 and 88 years. 86 patients (88.7%) of them developed reperfusion arrhytmias .[34] in other study , on 27 patients with acute myocardial infarction (MI) and their infarct-related coronary artery being completely occluded who received thrombolytic therapy or percutaneous transluminal coronary angioplasty, reperfusion was confirmed by immediate coronary angiography in 24. Reperfusion arrhythmias (RA) occurred in 19 (79.2%) of the patients, including ventricular arrhythmias in 13 (54.2%). Ventricular fibrillation and sustained ventricular tachycardia developed in 2 (8.4%) and accelerated idioventricular rhythm in 5 (20.8%). [23]

regarding side effect of thrombolytics, From whole of 52 patients received thrombolytic agent , only 1 (1%) patient developed side effect of therapy in form of GIT bleeding , . on a study analyzed the baseline characteristics, outcomes, and incidence of bleeding by location, severity, and treatment assignment among 41,021 patients in the GUSTO-I trial of thrombolysis for acute myocardial infarction. Of the 40,903 patients for whom there were complete data, 1.2% suffered severe bleeding and 11.4% experienced moderate hemorrhage at a variety of sites. The most common sources of bleeding were procedure related.[24]

regarding mortality rate in STEMI after thrombolytics , 1(1%)case die due to cardiac asystole . on other study , involved 41,021 patients treated with streptokinase or TPA or both , 1125(2.8%) deaths encountered within 24hours , and additional 1726 deaths within 30days .[32]

regarding cardiac arrythmia after thrombolytics , 2(4%) cases developed ventricular tachycardia , 1(1%) case developed ventricular fibrillation . in other study involved 3,491 patients , VT/VF were observed in 4.8% of patients. Impaired myocardial perfusion (TMPG 0/1/2) was associated with an increased incidence of VT/VF (7.1% vs. 2.6%). [33]

Conclusion

in this study , the response of STEMI was successful outcome in 82% based on presence one of three criteria involving patient get his symptoms improvement , reduction in amplitude of ST elevation to 50% of initial amplitude , or development of reperfusion arrhythmia . while failure rates reached to 18% in the enrolled samples.

short-term outcomes of patients receiving thrombolytic therapy were evaluated , most of patient got successful management safely and got home discharge , just 1(3%) developed complication in form of GIT bleeding controlled well with medically .

Recommendation

- Increase the samples to increase the accuracy of thrombolytic outcome in patient with STEMI .
- Obtaining parameters of the response to thrombolytics from coronary angiography .
- Increase the field of research beyond baqubah teaching Hospital to get more accuracy and avoidbias.

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Appendix

Frequency of inadequate response to thrombolytic in a sample of STEMI patients and their short-term outcome

ID number ..... Date of admission.....

Record number ..... Date of discharge .....

Patient telephone number .....

Name of patient ..... Age ..... occupation.....

Hight ..... weight .....

Smoker ☐ yes ☐ no

Alcohol consumption ☐ yes ☐ no

History of chronic disease ☐ HT ☐ DM ☐ CKD ☐ previous IHD ☐ stroke

History of COVID infection ☐ yes ☐ no

History of previous IHD (ACS,CSA) ☐ yes ☐ no

Symptoms at presentation ☐ typical chest pain ☐ loss of consciousness ☐ atypical symptoms

Time from symptoms onset till hospitalization ☐ <1hr ☐ 1-2hr ☐ 2-3hr ☐ >3hr

Time from symptoms onset till thrombolytic administration ☐ <1hr ☐ 1-2hr ☐ 2-3hr ☐ >3hr

Previous use of thrombolytics ☐ yes ☐ no

Previous use of anti-platelet ☐ yes ☐ no

Previous use of anticoagulant ☐ yes ☐ no

Localization of Ischemic area on ECG ☐ inferior STEMI ☐ anterior STEMI ☐ anterolateral STEMI

☐ Posterior STEMI ☐ anteroposterior STEMI

ST elevation amplitude ..... ☐ ≥ 1mm ☐ ≥ 1.5 mm ☐ ≥ 2mm

Lead with maximum STE .....

Residual LV dysfunction based on EF ☐ preserved ☐ 41-49% ☐ 30-40% ☐ <30%

short outcome of thrombolytics ☐ discharged ☐ death other .....

mechanical complication due to MI ☐ yes ☐ no in form of .....

ST resolution after thrombolytics ☐ >50% ☐ <50% resolving amplitude .....

Relieving symptoms ☐ yes ☐ no in form of .....