BIOSTATISTICAL STUDY OF CLINICAL RISK FACTORS OF MYOCARDIAL INFARCTION: A CASE-CONTROL STUDY FROM PAKISTAN

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ABSTRACT

Objective: This study is aimed at examining the degree of dependency of myocardial infarction (MI) on clinical risk factors and development of a biostatistical model for prediction of probabilities of MI in the presence of various variables.

Study Design: Analytical study (case-control study).

Place and Duration of Study: Data for this study is collected from various cardiac centers / hospitals from all the four provinces of Pakistan from February, 2013 to March, 2014.

Material and Methods: The study involves 2000 samples (1000 cases and 1000 controls) from all the four provinces of Pakistan. Both genders were included in the samples. Binary logistic regression analysis was performed to measure the probabilities of MI using statistical software SPSS. Odds Ratios were estimated for all the risk factors. Stepwise procedures were used.

Results: In this study all the risk factors i.e the Atherosclerosis (p<0.001), Ischemic heart disease (p<0.001), Hypertensive disorder (p<0.001), Diabetes mellitus (p<0.001), Deranged metabolic activity & obesity (p<0.001), Smoking (p=0.034), Consumption of alcohol (p=0.048), Family history (p=0.006) and Male gender (p<0.001) are proved statistically significant in the development of disease MI. Moreover all the clinical risk factors are positively associated with the response variable MI. Chest pain/coronary ischemia is found to be the most prominent symptom/etiology of MI.

Conclusion: In this study all the clinical risk factors are proved statistically significant in the development of Myocardial Infarction (MI).

Keywords: Case control study, Logistic regression, Myocardial infarction.

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INTRODUCTION

MI occurs when myocardial ischemia, a state of diminished blood supply to the heart at cellular level, exceeds a critical threshold and overwhelms myocardial cellular repair processes working naturally to maintain normal functioning and homeostasis. Ischemia and lack of oxygen at this critical threshold level for a prolonged period result in irreversible damage or death of myocardial cells known as Myocardial Infarction or cardiac necrosis[1]. The top most cause of global deaths is Cardiovascular disease (CVD) accounting for 17.3 million deaths/year and is likely to grow to more than 23.6 million by 2030[2]. In case of Pakistan the mortality due to heart disease is raised 135% from 1990 to 2013[3]. According to WHO (2011)[4] report the main contributors to the CVDs are the developing countries which are responsible for 82% of the global burden. The principal reason of these deaths is Myocardial Infarction (MI). MI is a disease caused by atherosclerosis. MI occurs if any of the heart muscles losses its blood supply or becomes dead[5]. This study includes the clinical risk factors of MI like Atherosclerosis, Ischemic heart disease (chest pain, shortness of breath etc.), Hypertensive disorder, Diabetes mellitus, Deranged metabolic activity & obesity, Smoking, Consumption of alcohol, Family history and Unhealthy life style (unhealthy food habits /eating habit & sedentary lifestyle/less physical

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activity, excessive intake of fried foods, less intake of fish & white meat to red meat ratio in food, also includes less intake of vegetables, less intake of fruits in diet as a part of dietary habits etc.) (see fig-1). All these variables are explored as significant variables in various studies like; Andersson & Waagstein (1993)[6], William B. K. (2000)[7], Nichols (2004)[8], Bibbins et al. (2004)[9], Kenchaiah (2009)[10], Hanif et al. (2010)[11] and Yusuf et al. (2004)[12].

This study aims to assess the association of each clinical risk factor with MI and fitting of appropriate statistical model for the clinical risk factors. This study also quantifies the impact of clinical risk factors of MI and highlights the most significant out of the lot that is liable for the life threatening disease. There are studies in context of Pakistan that covers the one or only few cities and hospitals but this study differs from others in covering all the four provinces in its sample size as the data is collected from all the large hospitals of each province. This study is likely to display the overall picture of the correlation between various clinical risk factors and myocardial infarction for the overall population of Pakistan.

MATERIAL AND METHODS

This case-control study was conducted at various cardiac centers/ hospitals of the country (table-1). The samples were collected from all the four provinces of Pakistan to make it more precisely reflective of the target population of the whole country. Samples from the four provinces were drawn using proportional allocation stratified sampling technique (table-2) according to the population size of each province. This data was collected between February, 2013 and March, 2014 from the hospitals shown in table-1. Average ages of the subjects were 59.52 ± 0.63 years.

The study involves 2000 subjects including 1000 cases and 1000 controls. The case control ratio is 1:1. Most of the controls are the ones who were present at the hospitals with their patients. Openepi statistical software is used to calculate the minimum sample size for both cases and controls at $\alpha = 5\%$ and $1 - \beta = 80\%$[13].

All the 2000 questionnaires were filled by the same investigator (principal author) to avoid bias. A subject was considered as a case if he/she suffered an MI at least once diagnosed by a cardiologist otherwise the subject was labeled as a control. Data for Atherosclerosis (narrowing of blood vessels due to bad fatty acids) was measured from HDL/LDL levels on the following scale; HDL was abnormal if cholesterol <40mg/dl and LDL was abnormal if cholesterol >160 mg/dl. Hypertensive disease was measured from higher ranges of blood pressure on the following scale; A subject is considered as hypertensive if the Systolic Blood Pressure (SBP) >140 mmHg or Diastolic Blood Pressure (DBP) was >90mmHg. Diabetes mellitus is measured from serum glucose levels in fasting condition; Blood sugar was taken normal if Fasting Blood Glucose (BSF) is <120 mg/dL and if BSF was >120 mg/dL on a series of consecutively taken results for a fortnight with atleast 3 or more deranged readings, the subject was counted as a diabetic patient. Deranged metabolic activity & obesity was measured from BMI as; BMI was normal if (18.5 < BMI < 25) Kg/m^2 and a person is obese if BMI > 25 Kg/m^2. A subject was consider smoker if he/she takes at least one cigarette per day[14]. A subject was considered as drinker if he/she takes one liter alcohol at least once per week. Family history was asked from the subjects if any of their close blood relative has had MI. Unhealthy life style was measured on account of unhealthy food habits, excess intake of junk and fried foods, less frequency of taking fish, white meat, vegetables and fruits in diet. Abnormal sleep patterns and sedentary life style with lack of enough physical activity (fig-1) also constitute unhealthy lifestyle. Ischemic heart disease is measured from narrowing of cardiac vessels and ischemia leading to often chest pain and frequent shortness of breath.

SPSS-16 was used for analysis. Data was collected from both the genders and out of total 2000 subjects 1116 were females & 884 were

males. The study involved myocardial infarction (MI) as a binary response variable (yes/no) and Atherosclerosis, Ischemic heart disease, Hypertensive disease, Diabetes mellitus, Deranged metabolic activity and obesity, Smoking, Consumption of alcohol, Family tendency and Unhealthy life style as explanatory variables. Binary logistic regression procedures were used applying SPSS to assess the probability of MI. Odds Ratio was estimated to see the risk of explanatory variables on MI. Stepwise procedures was sequential in the sense that they assume a current model and look to add to, or delete terms one at a time from that model (Brown, 1978)[15]. In today's world the medical research often involves binary response variable and the use of logistic regression is frequent in this field.

Table-1: List of the hospitals from all the provinces of Pakistan.

Name of Hospital	City	Province
PIMS	Islamabad	Federal Capital
Lady Reading Hospital	Peshawar	KPK
Rawalpindi Institute of Cardiology	Rawalpindi	Punjab
Punjab Institute of Cardiology	Lahore	Punjab
Jinnah Hospital	Karachi	Sind
Bolan Medical Complex	Quetta	Balochistan
Civil Hospital	Quetta	Balochistan

Table 2: Samples size from provinces of the Pakistan.

Province	Sample Size	Percent
Punjab	1000	50.0
KPK	456	22.8
Sindh	400	20
Balochistan	144	7.2
Total	2000	100.0

Table 3: Model efficiency diagnostics.

Omnibus test	Nagelkerke's R-squares	Hosmer & Lemeshow test
$p<0.001$	0.932	$p= 0.67$

RESULTS

In this study 2000 subjects were analyzed comprising of 1000 cases and 1000 controls. Omnibus test reflects (table-3) the appropriateness of the model and its results for the fitted model in this study certify that the model is appropriate as the p-values are significant ($p< 0.05$).

Nagelkerke's R-squares for the fitted binary logistic regression model was 93.2% (table-3) shows that the explanatory variables (risk factors) were explaining the response variable (MI) very well.

Hosmer & Lemeshow (2013)[16] test detects if there is any misspecification in the predictive capacity of the model and for a good model Hosmer & Lemeshow (2013) test must be insignificant (p-value > 0.05). In this study p=0.67 (table-3) and Hosmer & Lemeshow test confirms that there are no significant misspecifications in predictive capacity of the binary logistic regression model.

Table-4 contains those clinical risk factors in the binary logistic regression model which are significant and whose p-values are less than 0.05. The Atherosclerosis, cardiac ischemia (Shortness of breath, chest pain), Hypertensive disorder, Diabetes Mellitus, Smoking, Obesity, Less physical Activity, Family history are proved significant in the development of MI in this

study. Mostly the coefficients (B) of the risk factors are positively associated to the response variable MI. These positive signs indicate that the patients with these risk factors are at higher risk of developing MI than their respective controls. For Atherosclerosis the odds ratio (OR) tells that by keeping all the other risk factors constant a patient of Atherosclerosis is 2.82 times at higher risk than a normal / healthy person. Similarly the Odds Ratios (OR) for the patients experiencing the cardiac ischemia exhibited as shortness of breath is 2.745 times & chest pain (16.83 times), Hypertensive disorder (6.598 times), Diabetes mellitus (6.459 times), Intake of alcohol (2.352 times), Smoking (1.407 times), Obesity (8.084 times), Male gender (2.934 times), Less physical activity (0.720 times), Less intake of fish (0.683 times), Less intake of vegetables (0.608 times) and Family history (2.142 times) are found at higher risk of developing MI than their respective controls. Chest pain / cardiac ischemia looks very prominent and most significant symptom / etiology in this study.

Table-5 contains the variables which as per results drawn from this study are proved as insignificant in development of MI. The etiologies which are insignificant are: Excess of fried food and less intakes of fruits.

Fitted Logistic Regression Model

Theoretical model for this study is17, f (z) = ez / (1 + ez); where z = $\beta 0 + \sum \beta ixi$ for i = 1, 2, … k. In this study k = 11 and z = Logistic Regression model. Putting all the values we get our final binary logistic regression model as, f (MI) = 1 / (1 + e-z) , Where Z = -10.368 + 1.04(HLDL) + 1.01(BR) + 2.83 (CP) + 1.89 (HBP) + 1.86 (DM) + 0.34 (TOB) + 2.09 (BMI) + 1.08 (GEN) - 0.33 (PA) - 0.38 (FS) - 0.5 (VG) + 0.76 (FH).

Table- 4: Significant risk factor variables in the model.

Risk Factors	Coefficient (B)	*p*-value	OR
Atherosclerosis (HLDL)	1.037	< 0.001	2.820
Shortness of breath (BR)	1.010	0.001	2.745
Chest Pain / ischemia (CP)	2.824	< 0.001	16.83
Hypertensive Disorder (HBP)	1.887	< 0.001	6.598
Diabetes Mellitus (DM)	1.865	< 0.001	6.459
Intake of Alcohol (AL)	0.855	0.048	2.352
Tobacco / Smoking (TOB)	0.341	0.034	1.407
Obesity (BMI)	2.090	< 0.001	8.084
Male gender (GEN)	1.078	< 0.001	2.938
Less Physical Activity (PA)	- 0.328	0.016	0.720
Less intake of Fish (FS)	- 0.381	0.060	0.683
Less intake of Vegetables (VG)	- 0.498	0.013	0.608
Family History (FH)	0.762	0.006	2.142
Constant	-10.368	< 0.001	

Table-5: Insignificant risk factor variables in the model.

Risk / Etiology	*p*-value
Excess of Fried Food	0.844
Less intake of Fruits	0.196

DISCUSSION

Cardiovascular diseases are the major reason of mortality around the world particularly in the developing countries including Pakistan. Myocardial infarction is the foremost cause of death in the United States and in most developed states throughout the world[18]. Around 450,000 people in the United States die from coronary

disease per year[19]. However the survival rate for U.S. patients hospitalized with MI is approximately 95% and this is because of extensive medical research related to emergency medical care and treatment options.

This study focused on clinical variables only and most of the risk factors proved very important in the development of the disease. Severe myocardial ischemia leading to MI can occur as a result of increased myocardial metabolic demand, decreased supply of oxygen and nutrients to the myocardium through the coronary circulation or both. Furthermore as per the study conducted by Bolooki & Askari (2010)[19] an interruption in the supply of myocardial oxygen and nutrients also happens when a thrombus is superimposed on an ulcerated or unstable atherosclerotic plaque and results in coronary occlusion. A severe or high-grade (>75%) coronary artery stenosis caused by atherosclerosis or coronary vasospasm can also diminish the supply of oxygen and nutrients to the myocardium and precipitate an MI. Extremes of physical exertion, hypertension and aortic valve stenosis are the conditions that increase the myocardial metabolic demand causing an MI to trigger due to unmet needs of oxygen and nutrients at cellular level. Cardiac valve pathologies and low cardiac output leading to low coronary perfusion, can also precipitate MI. Hyperlipidemia; Elevated levels of total cholesterol, LDL or triglycerides cause an increased risk of coronary atherosclerosis and thus MI. Lower levels of HDL less than 40 mg/dL pose a higher risk of MI. In this regard a full summary of the National Heart, Lung and Blood Institute's cholesterol guidelines is available online[20].

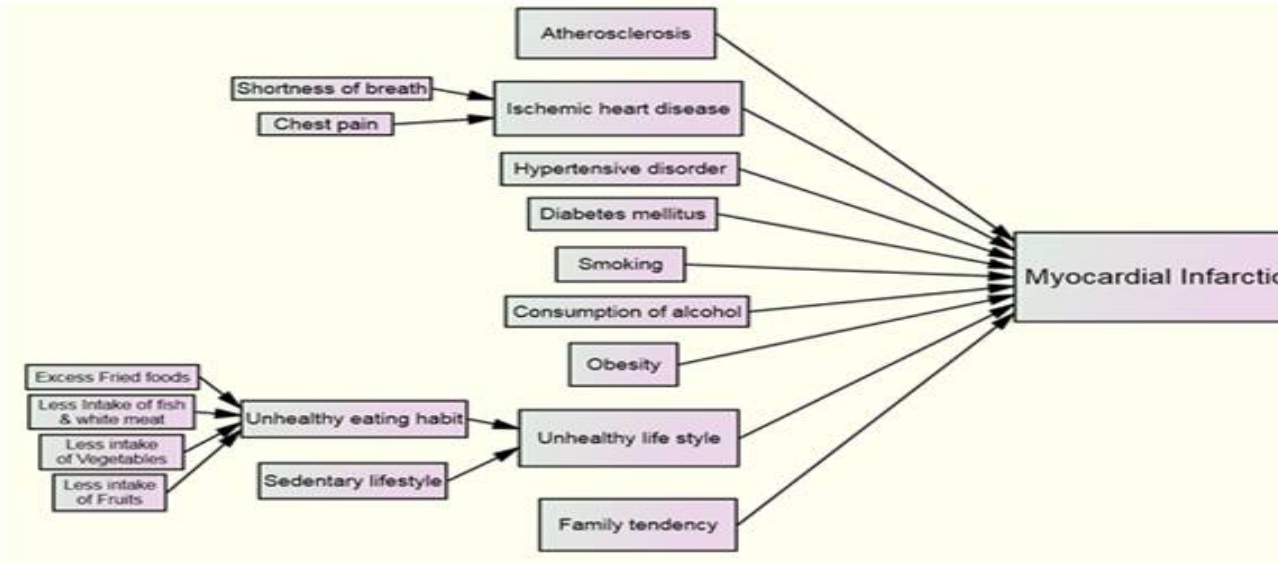

Figure-1: Flow chart of clinical risk factors of myocardial infarction.

Diagnosis of MI is based on the clinical history, ECG, and blood test results, especially creatine phosphokinase (CK), CK-MB fraction, and troponin I and T levels. Aspirin, nitrates, and beta blockers are very important to be used as part of treatment options early in the management of MI for all patients1. For those patients who depict ST Elevation changes of MI in ECG (STEMI) coronary angiography with angioplasty and stenting is advisable within 90 minutes of arrival of the patient at health facilities who bear good cardiac and surgical expertise in these procedures. Fibrinolytic therapy should be used as an alternative option in cases where early angiographic intervention is not possible due to some reasons. Prognosis of the disease and

Outcome following an MI is determined by the infarct size and location, and by timely medical intervention. Following recovery from the acute attack, the post-discharge management of the MI patient requires strict adherence to long term medication, pharmacotherapy, regular follow up of the disease and permanent lifestyle modification.

The study of impact of all clinical variables on MI was very important to be explored because these risk factors prevail very commonly in almost all the societies of the world and in particularly in the low socio-economic environment where the common people are always at risk of unhealthy life style, hypertensive disorder, diabetes etc. This study reveals Chest pain as a result of cardiac ischemia as the most prominent symptom / etiology of MI.

Qureshi et al. (2011)[5] surveyed a sample of 208 collected from Peshawar including clinical risk factors of CVD and found blood sugar and blood pressure as significant risk factors. Studies by Andersson & Waagstein (1993)[6] and William B. K. (2000)[7] highlighted hypertension, diabetes mellitus and blood sugar as the main risk factors of heart failure. Patients with DM are at greater risk of heart attack and DM is responsible for 3.1% rate of such incidents6. Bibbins et al. (2004)[9] says that diabetes mellitus (DM) is the biggest individual risk factor of heart disease. Patients with diabetes bear greater risk of atherosclerotic vascular disease in the heart as well as in other vascularized areas. Diabetes increases the risk of MI because it increases the rate of atherosclerotic progression and adversely affects the lipid profile and facilitates formation of atherosclerotic plaque.

Hypertension is strongly associated with an increased risk of MI both with systolic and diastolic hypertension. In old age hypertension is even worse to heart and responsible for at least 70 percent of heart disease[7].The control of hypertension with strict compliance of proper medication and adoption of lifestyle modifications reduces the risk of MI significantly. A full summary of the National Heart, Lung and Blood Institute's guidelines are available online[21].

Some specific components of tobacco are found to damage the walls of the blood vessels. The body's natural response to this type of injury triggers the atherosclerosis or atherosclerotic plaque formation and its progression, thus increasing the risk of MI. A small study in a group of volunteers showed that smoking acutely increases platelet thrombus formation to target the stenotic vessels leading to low perfusion ischemia, independent of aspirin use[22]. A family history of prevalence of coronary disease increases an individual's risk of MI. The cause of familial coronary incidences is genetic components and self adopted unhealthy lifestyle practices such as sedentary life, lack of exercise, smoking, and high-fat diet intake. Unhealthy food habits and lifestyles are pushing people towards obesity, hypertension, diabetes mellitus etc. Obesity is highly correlated to cardiac failure and its relative risk verses the normal weight subjects10. Hanif et al. (2010)[11] surveyed a sample of 364 subjects collected from Lahore including clinical and non-clinical variables showed in their study that diabetes mellitus and obesity were significant risk factors of heart disease. Yusuf et al. (2004)[12] in their research discussed abdominal obesity as the most significant risk factor of MI and those with such obesity have 200% chance of MI as compared to non obese whereas in our study this chance is 800%. Sricharan et al. (2012)[18] evaluated obesity, diabetes mellitus and chest pain as the significant variables of MI. Qureshi et al. (2011)[5] surveyed a sample of 208 collected from Peshawar including clinical and non-clinical risk factors of CVD and found blood sugar and blood pressure as significant risk factors. This study is the latest in context of Pakistan covering all the country as well as all the major clinical risk factors. The findings (significance of risk factors) of this study are consistent with Hanif et al. (2010)[11], Qureshi et al. (2011)[5], Yusuf et al. (2004)[12], Sricharan et al. (2012)[18] and Boloonki & Askari (2010)[19] however the odds ratios of risk factors of MI are higher than these cited studies.

People should regularly visit cardiologist to keep themselves updated regarding health and status of heart function. All the clinical variables/risk factors of MI are very injurious to health so incase of any symptom of any of the risk factors an immediate cardiac consultation and lifestyle modification is required to reduce the risk of an MI.

CONCLUSION

The study statistically proved that the risk of MI increases significantly in the presence of clinical risk factors; atherosclerosis, ischemic heart disease, hypertensive disorder, diabetes mellitus, deranged metabolic activity/obesity, smoking, consumption of alcohol, male gender, family history and unhealthy life style.

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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