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CARDIOVASCULAR DISEASE RISK PREDICTION IN PATIENTS WITH BIPOLAR AFFECTIVE DISORDER-A CROSS SECTIONAL STUDY

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Abstract:

Introduction: In recent years, there has been increasing recognition of the influence of mental health on cardiovascular diseases (CVD) and their risk factors. CVD causes premature mortality and morbidity, when co occurs with psychiatric illnesses, the overall mortality and morbidity is further increased, thus decreasing the life span and quality of life of the individual. In Bipolar disorders (BD), the most frequent cause of death is with CVD. Cardiovascular risk factors such as obesity, metabolic syndrome and diabetes mellitus type II (T2DM) disorder are under-recognized and sub optimally treated and these risk factors independently exert deleterious effects on its course.

Material and Methods: The study employed a cross-sectional design and was conducted at Bhaskar General Hospital, Yenkapally (V), Moinabad (M), R.R District. A total of 150 consecutive consenting adult men and women, previously diagnosed with Bipolar Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and attending the hospital for at least one year, were recruited for this study between November 2013 and July 2015. Additionally, 50 age- and sex-matched controls, with no past, present, or family history of psychiatric illnesses, were recruited during the same period. For the purpose of assessment using the Framingham Heart Study criteria, only individuals aged 30-74 years were included in the study.

Results: Patients with bipolar disorder exhibited a significantly higher risk of developing cardiovascular outcomes, including myocardial infarction (MI) and cardiac death, over a 10-year period. This was evidenced by a Framingham cardiovascular risk score of 8.966, compared to 6.088 in the control group

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(Figure 27). The Pearson chi-square test for risk (P=0.006) indicated a significant difference between the two groups.

Conclusion: Aggressive interventions to correct or improve the metabolic parameters associated with metabolic syndrome and CVD in bipolar disorder are necessary, ideally within the first ten years of detection.

Keywords: Bipolar disorders, cardiovascular diseases, diabetes mellitus, T Framingham cardiovascular risk score.

INTRODUCTION

The majority of the world's population of 450 million people who suffer from a mental problem live in developing countries. Over 7% of the Indian population suffers from a psychiatric disorder. This figure increases substantially if we consider other common mental conditions such as substance use disorders, anxiety, depression and dementia. It is pivotal to address their needs, while being sensitive to their physical health.[1] The lifespan of people with severe mental illness (SMI) is shorter compared to the general population. This excess mortality is mainly due to physical illness. The prevalence rates of different physical illnesses as well as important individual lifestyle choices, side effects of psychotropic treatment and disparities in health care access, utilization and provision that contribute to these poor physical health outcomes[2].

In recent years, there has been increasing recognition of the influence of mental health on cardiovascular diseases (CVD) and their risk factors.[3] CVD causes premature mortality and morbidity, when co occurs with psychiatric illnesses, the overall mortality and morbidity is further increased, thus decreasing the life span and quality of life of the individual.[4] The World Health Organization lists Bipolar disorder as the sixth leading cause of disability in the world. Those diagnosed with Bipolar disorder can face up to ten years of coping with symptoms before receiving an accurate diagnosis. Life expectancy is decreased for those suffering from Bipolar disorder by 9.2 years. Bipolar disorder affects men and women equally. An equal number of men and women develop bipolar illness and it is found in all ages, races, ethnic groups and social classes.[5]

In Bipolar disorders (BD), the most frequent cause of death is with CVD.[6] Cardiovascular risk factors such as obesity, metabolic syndrome and diabetes mellitus type II (T2DM) disorder are under-recognized and sub optimally treated and these risk factors independently exert deleterious effects on its course.[7] The age of onset of diabetes mellitus (DM) in individuals with a SMI seems to be about 10-20 years earlier than in the general population.[8] Type 2 diabetes mellitus (T2DM) rates are three times higher in patients with bipolar disorder (BD), compared to the general population. This is a major contributing factor to the elevated risk of cardiovascular mortality, the leading cause of death in bipolar patients. There may be shared pathophysiology linking the two disorders, including hypothalamic-pituitary-adrenal and mitochondrial dysfunction, common genetic links, and epigenetic interactions. Life-style, phenomenology of bipolar symptoms, and adverse effects of pharmacotherapy may be contributing factors. Patients with BD and T2DM have a more severe course of illness and are

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more refractory to treatment. Control of their diabetes is poorer when compared to diabetics without BD.[9] About 12% of people receiving antipsychotic medication were affected by DM.[10] Antipsychotics and Mood stabilizers appear to contribute to DM both indirectly, by inducing weight gain, and directly, by promoting insulin resistance.[11] Mortality from natural causes among patients with bipolar spectrum disorders was 35% higher than a comparison group and was mainly attributed to excess smoking and non recreational physical activity.[12]

AIMS AND OBJECTIVE

To estimate the Framingham risk scores for general cardiovascular disease events (10 years risk prediction) among patients with a diagnosis of bipolar affective disorder.

Inclusion criteria – Subjects:

- Patients who provide informed consent.
- Subjects between the ages of 30 to 74 years old (according to the requirement of Framingham heart study) and without Cardio vascular disease (CVD) at the baseline examination.
- Patient with diagnosis of bipolar affective disorder and who has attended the hospital at least 3 or 4 times in one year).
- Duration of illness at least 1 year with current status of no active manic or depressive episodes.

Inclusion criteria – Control group:

- Subjects providing informed consent.
- Subjects who had no past, present and family histories of psychiatric illnesses

Exclusion criteria - Either group:

- Patients with severe renal disease, severe hepatic dysfunction, other severe medical disorder. (The rationale for excluding these medical conditions is that these conditions have an impact on blood pressure (BP), or lipids. However, people whose Blood Pressure is controlled with medications, or whose cholesterol is treated with cholesterol lowering agents were included).
- Pregnant women.
- Presence of co morbidity that may compromise the interpretation of the Framingham risk scores.
- Presence of organic mental disorder.

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PATIENTS AND METHODS

The study employed a cross-sectional design and was conducted at Bhaskar General Hospital, Yenkapally (V), Moinabad (M), R.R District. A total of 150 consecutive consenting adult men and women, previously diagnosed with Bipolar Disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), and attending the hospital for at least one year, were recruited for this study between November 2013 and July 2015. Additionally, 50 age- and sex-matched controls, with no past, present, or family history of psychiatric illnesses, were recruited during the same period. For the purpose of assessment using the Framingham Heart Study criteria, only individuals aged 30-74 years were included in the study.

Methods of Data Collection

The study received approval from the institutional ethics committee. Informed consent was obtained from all subjects prior to their enrollment in the study.

Data Collection Instruments

A detailed case history was recorded using separate proforma for cases and controls. The proforma included the following information:

- Socio-demographics: Data on age, gender, education, and occupational status.
- Smoking History: History of cigarette smoking and nicotine dependence, assessed using the Fagerstrom Smoking Questionnaire.
- Psychiatric Diagnosis: Diagnosis of psychiatric disorders was made using the DSM-5 diagnostic criteria.
- Anthropometric Measurements: Height, weight, waist, and hip circumference were measured using standardized procedures. Body Mass Index (BMI)and Waist-Hip Ratio (WHR) were calculated for each subject.
- Blood Pressure: Blood pressure was measured using a sphygmomanometer on the right upper limb in a sitting position.

Laboratory Assays

A single venous blood sample was collected from each subject in evacuated tubes after an overnight fast of 12 to 14 hours. The samples were analyzed for total cholesterol (TC) and high-density lipoprotein (HDL) in an accredited laboratory.

CVD RISK ASSESSMENT:

The cardiovascular risk for each subject was calculated using the Framingham 10 year risk calculator available on the webpage https://www.framinghamheartstudy.org/risk-functions/cardiovascular-disease/10-year-risk.php#.[13] Computed percentage risk estimates for the number of outcomes over the 10 year period were taken. This 10 year risk calculator is best suited for individuals free of CHD. Estimation of the risk differs for men and women. The risk factors such as age, total cholesterol, HDL, SBP, treatment for hypertension and smoking status are considered to arrive at a score, which calculates the hard coronary heart disease outcomes. Each factor has been given a point and the Framingham risk score is arrived by addition of the points according to the subjects' age, levels of TC and HDL, systolic blood pressure (SBP), treatment for

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hypertension and smoking status. The point total is then correlated with the 10 year risk (as shown in the annexure V).[14]

Framingham risk scoring system

The original Framingham Risk Score had been published in 1998. The next version was published in 2002. Current version of the Framingham Risk Score was published in 2008. The publishing body is the Adult Treatment Panel III (ATP III), an expert panel of the National Heart, Lung, and Blood Institute, which is part of the National Institutes of Health (NIH), USA.[15,16] The Framingham Risk Score is a gender-specific algorithm used to estimate the 10-year cardiovascular risk of an individual. The Framingham Risk Score was first developed based on data obtained from the Framingham Heart Study, to estimate the 10-year risk of developing coronary heart disease.[17] In order to assess the 10- year cardiovascular disease risk, cerebrovascular events, peripheral artery disease and heart failure were subsequently added as disease outcomes for the 2008 Framingham Risk Score, on top of coronary heart disease.[13] Cardiovascular risk scoring systems give an estimate of the probability that a person will develop cardiovascular disease within a specified amount of time, usually 10 to 30 years.[18]

OBSERVATIONS AND RESULTS

Characteristics of participants:

Data pertaining to the two study cohorts were tabulated and analyzed at the end of the study period (table 1). The groups were well matched in terms of age and gender. Both the groups differed significantly in terms of education, occupation, marital status, and socio economic status, presence of co morbid medical illness, family history of medical illness, waist circumference, and diastolic blood pressure, levels of total cholesterol, HDL and Framingham CVD risk score.

Our study has shown that patients with bipolar disorder have a higher risk of developing an adverse cardiovascular outcome in 10 years compared to the control group.

Table 1: Showing Characteristics of participants in the study

	Subjects with bipolar disorder (n=150)	Controls (n=50)	P- values
Age, years: Mean (S.D.)	44.38(11.290)	43.66(10.293)	0.690
Gender: n (%) Male Female	 83(55) 67(45)	 29(58) 21(42)	0.742

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Education: n (%) Primary Secondary Graduate Post graduate	 9(6) 75(50) 66(44) 0(0)	 8(16) 15(30) 24(48) 3(6)	0.001***
Employment: n (%) Unemployed Employed	 84(56) 66(44)	 19(38) 31(62)	0.027**
Marital status: n (%) Married Unmarried	 123(82) 27(18)	 48(96) 2(4)	0.015**
Socio economic status: n (%) Upper Upper middle Middle Lower middle Lower	 3(2) 33(22) 96(64) 18(12) 0(0)	 3(6) 13(26) 29(58) 0(0) 5(10)	0.000***
Smoking status: n (%) Absent Present	 114(76.7) 36(23.3)	 40(80) 10(20)	0.56
FSQS: Mean	1.04	0.62	0.298
Duration of illness in yrs: Mean(S.D.)	9.14(6.493)		
Duration of treatment in yrs: Mean(S.D.)	2.50(0.775)		

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Distribution of pharmacotherapeutic agents: (%)	Olanzapine (5.3%) Valproate, Quetiapine (10.7%) Valproate, Risperidone, Lithium, Quetiapine (2%) Valproate, Olanzapine (20%) Valproate, Quetiapine, Olanzapine (4%) Lithium, Olanzapine (14%) Lithium, Risperidone (4%) Risperidone, Valproate (15.3%) Olanzapine, Risperidone (4%) Risperidone, Valproate, Aripiprazole (2%) Risperidone (4%) Olanzapine, Lithium, Valproate (4%) Risperidone, Valproate, Lithium (2%) Valproate (8.7%)		
Medical history: n (%) Diabetes Hypertension Both Nil	 3(2) 36(24) 11(7.3) 100(66.7)	 7(14) 5(10) 1(2) 37(74)	 0.002***
Treated for medical Illness: n (%) Yes No	 47(31.3) 103(68.7)	 11(26) 39(74)	 0.27
Family history of medical Illness: n (%) Diabetes Hypertension Both Nil	 6(4) 26(17.3) 12(8) 106(70.7)	 10(20) 6(12) 7(14) 27(54)	 0.001***
Height: Mean(S.D)	1.660(0.0868)	1.636(0.0773)	0.082*
Weight: Mean(S.D)	70.83(11.449)	69.34(11.717)	0.428

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Body mass index: Mean(S.D.)	25.6077(3.888)	25.9568(3.978)	0.585
Waist circumference: Mean(S.D.)	91.17(15.369)	84.41(21.678)	0.017**
Waist hip ratio: Mean(S.D.)	0.9075(0.06859)	0.9112(0.08966)	0.763
Systolic Blood Pressure: Mean(S.D.)	122.17(8.027)	122.60(9.216)	0.754
Diastolic Blood Pressure: Mean(S.D)	79.01(7.363)	82.40(6.565)	0.004***
Total cholesterol: Mean(S.D.)	169.33(31.614)	158.02(15.506)	0.016**
HDL: Mean(S.D.)	37.49(9.633)	46.68(5.644)	0.000***
Framingham CVD Risk scores in next 10 yrs: Mean	8.966	6.088	0.006***
Risk type: n (%) Low Moderate Moderately high High	 73(48.7) 38(25.3) 23(15.3) 16(10.7)	 32(64) 9(18) 5(10) 4(8)	 0.312

*Proportions significantly different at 90% (P<o.1)
**Proportions significantly different at 95% (P<o.05)
***Proportions significantly different at 99% (P<o.01)

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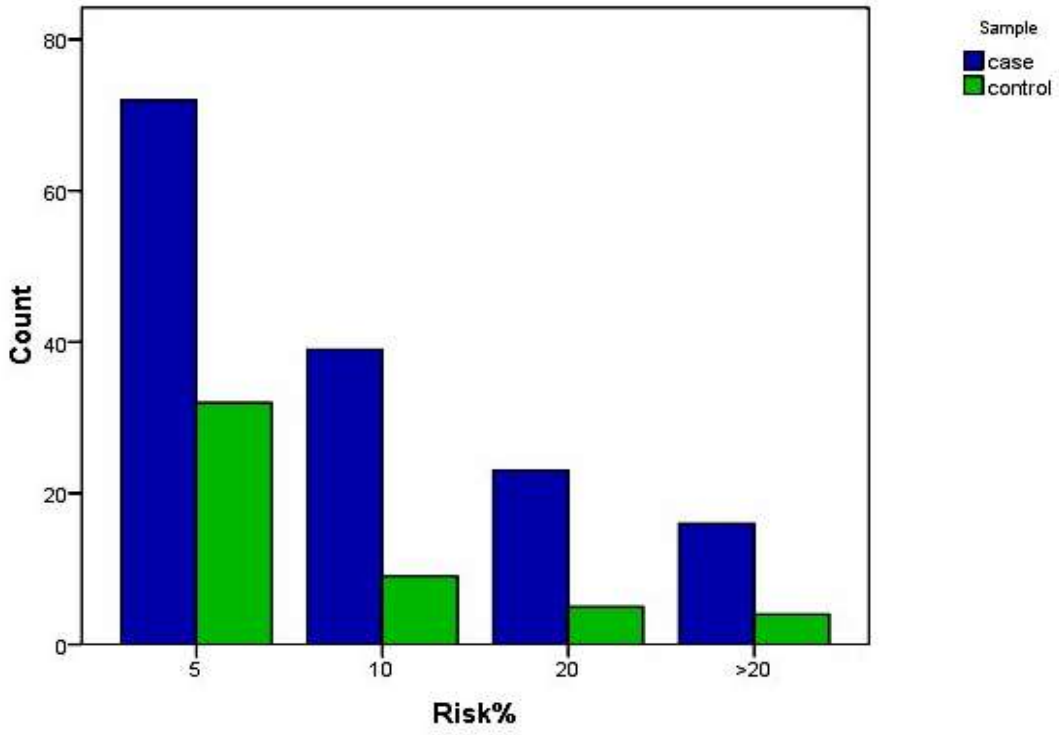
Distribution of the study population according to their Framingham risk score (risk at 10 years)



Patients with bipolar disorder showed to have a higher risk of developing cardio vascular outcomes (in 10 years) such as MI, cardiac death with a Framingham cardio vascular risk score of 8.966 than that of controls (6.088) . Pearson chi square for risk (P=0.006) showed the significant variation between the two groups.

DISCUSSION

The study is an attempt to evaluate the Cardio vascular risk factors in individuals suffering from Bipolar affective disorder by using Framingham scale. The previous studies have been compared with the results found in this study.

CVD risk score:

The risk of future CVD was 8.966 in our study population. This was comparatively higher when compared to the studies by Maria *et al* 2009 (7.75)[19], Montes *et al* 2009 (7.3)[20], Correll *et al* 2008 (4.7).[21] Studies conducted by Birkenaes *et al* 2007[22], Sloka *et al* 2012[23] showed that their study population had CVD risk of >10 and <20. This could be due to the variation in the study sample size and socio demographic profile of the study population.

There was a significant increase in the ten year Framingham cardiovascular risk scores in patients suffering from bipolar disorder when compared to normal controls. Among the patients with bipolar disorder 48.7% showed low risk, 25.3% showed moderate risk, 15.3% showed moderately high risk and 10.7% of the patients showed high risk. A study conducted by Ford ES *et*

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al showed that 81.7% of patients had low risk, 15.5% had intermediate risk, and 2.9% had high risk. High risk category was more in our study and the risk was increasing with advanced age, male gender, primary education, unemployment, unmarried, lower middle socio economic status, smoking, long duration of psychiatric illness, co morbid medical illness, increase in waist hip ratio, high total cholesterol and low HDL.[24] In a study by Murray DP *et al*, the individuals with bipolar disorder face a nearly two-fold increased risk of cardiovascular mortality relative to the general population.[25]

Sowden & Huffman 2009[26] study reported that bipolar disorder (BD), depression, anxiety disorders and schizophrenia have all been identified as risk factors for the onset and progression of cardiovascular disease (CVD). Baune *et al* 2006[27] study reported that Bipolar I disorder, which occurs in approximately 1% of the general population is significantly more prevalent in patients with cardiac disease. According to Tsai *et al* 2005[28] and Carney *et al* 2006[29] studies individuals with BD die younger than their peers, due largely to an increased prevalence of medical co-morbidities and much of this excess mortality stems from CVD. In fact, patients with BD are up to twice as likely to die from cardiovascular causes as their counterparts in the general population.

Conclusions and Summary

This study was designed to collect data on cardiovascular risk in patients with bipolar disorder within a typical clinical setting, utilizing the Framingham 10-year cardiovascular risk estimation. We successfully recruited age- and sex-matched samples. The risk of developing a future cardiovascular event was found to be 8.966% in patients with bipolar disorder, compared to 6.088% in the control group. Consequently, we conclude that patients with bipolar disorder have a higher risk of cardiovascular events compared to the control group.

Our findings corroborate the results of several other studies and provide additional insights into the cardiovascular disease risk associated with bipolar disorder. Factors such as a higher age at onset of illness, male gender, primary education, unemployment, unmarried status, lower middle socioeconomic status, smoking, long duration of psychiatric illness, comorbid medical conditions, increased waist-hip ratio, high total cholesterol, and low HDL were positively associated with an increased future cardiovascular disease (CVD) risk.

Aggressive interventions to correct or improve the metabolic parameters associated with metabolic syndrome and CVD in bipolar disorder are necessary, ideally within the first ten years of detection.

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