Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/kadpx594

FAMILY HISTORY OF PREMATURE CORONARY ARTERY DISEASE AS AN INDEPENDENT PREDICTOR OF DISEASE SEVERITY: AN OBSERVATIONAL SINGLE-CENTRE STUDY

Dr. Muhammad Musa[1], Dr. Farhat Ullah Khan[2*], Dr. Naeem Khan[2], Dr. Muhammad Idrees Khan[2], Dr. Ayesha Bibi[3], Dr. Rahim Dil Khan[4]

[1]Department of Medicine and Allied, Khalifa Gul Nawaz Teaching Hospital, Bannu, Pakistan.
[2*,2,2]Department of Cardiology, Hayatabad Medical Complex, Peshawar, Pakistan.
[3]Department of Cardiology, Ayub Teaching Hospital, Abbottabad, Pakistan.
[4]Fellow Interventional Cardiology, Hayatabad Medical Complex, Peshawar, Pakistan

***Corresponding Author:** Dr. Farhat Ullah Khan
*Department of Cardiology, Hayatabad Medical Complex, Peshawar, Pakistan.
Email: bleedgreen53.fk@gmail.com

ABSTRACT

Introduction: Coronary artery disease (CAD) is still a critical and prevalent global health concern, and early onset further increases the threat. It has been established that the history of premature CAD depends on family significantly and is an independent risk factor that determines the development and course of the disease.

Objective: To determine whether a family history of premature CAD is an independent predictor of angiographic disease severity in patients diagnosed with CAD at a tertiary care hospital in Pakistan.

Materials and Method: This cross-sectional study conducted at multi centers including Department of Cardiology, Ayub Teaching Hospital Abbottabad and Hayatabad Medical Complex Peshawar from June 2023 to June 2024. A total of 320 patients being referred for coronary angiography were evaluated in terms of disease severity using the Gensini score. Data were analyzed using SPSS v26.

Results: Individuals with a positive family history had higher Gensini scores (74.2 ± 18.6) and triple-vessel disease rates (39.4%) than those without (21.9%, 58.9 ± 16.3; $p<0.001$).

Keywords: Pakistan, Gensini score, premature CAD, family history, coronary artery disease, and disease severity.

INTRODUCTION

CAD is a common debilitating disease that has a significant impact on global health, particularly because of its early occurrence in today's society. However, numerous epidemiological studies of CAD primarily identify hypertension, diabetes, smoking, and dyslipidemia as some of the traditional CAD risk factors, though the focus is now shifting to one's genetic makeup, especially a family history of early onset of CAD (1). Imaging like cardiac CT has enabled physicians to 'snap pictures' of patients with such family histories, which are evidence of subclinical atherosclerosis, explaining the pathophysiology pattern of genetically susceptible patient populations (1). Pakistanis and Indians have a higher incidence of CAD and are more likely to present at a younger age than patients from Western countries. Research works that have been carried out in tertiary hospitals have revealed a high incidence of acute coronary syndrome (ACS) in persons below 55 years of age, many of whom

described hereditary tendencies to cardiovascular calamities (2). This association may reflect both genetic susceptibility and exposure to environmental risks, and it is essential to distinguish family history as an independent and modifiable risk factor.

While previous studies have focused on other aspects of CAD, including the treatment and prognosis of the disease in certain groups, including infants with cardiac interventions (3) or long-term statin users (4), the impact of genetic predisposition on the disease severity remains inconclusive. There are several strengths to such analysis, and the best approach is using existing multi-center observational studies, as these reduce inconsistencies in data collection and control other cofactors (5). In the context of Pakistan, metabolic syndrome and dyslipidemia are very common, and risk stratification due to genetic and familial factors becomes even more crucial. A cross-sectional study from a tertiary care hospital in Pakistan independently validated the importance of FHR in increasing cardiovascular risk, irrespective of other metabolic factors (6). Additionally, there is a significant interaction between both lipoprotein(a) and familial CAD in the early onset and the severity of coronary disease, as the RELACS study portrays (7). Such evidence implies the need for tiered screening techniques that combine genetic susceptibility tests with conventional risk-factor profiles.

Family history of the disease can also play a role in their propensity to arrhythmias and structural disorders, for instance, Lamin A/C gene mutation, which earlier studies observed to be linked to adverse cardiovascular events from observational studies over two decades (8). Moreover, patients suffering from premature ventricular contractions and complex arrhythmic morphology have similar genetically determined electrophysiological features that strengthen the link between heredity and CAD complications (9). The importance of family patterns is further underscored by scientific studies that use matched control to reduce bias, such as in psychiatric and cardiovascular studies dealing with cholinergic activity(10). Such protocols show the endurance of multi-center observational-based designs in excluding confounding factors of FHS with other clinical factors.

Another area of interest is CAD's association with peripartum cardiomyopathy, which shows that valuable echocardiographic measurements are linked with a maternal history of cardiovascular disease, showing risk continuity across generations (11). Besides, there are screening programs for example, the UNISCREEN pilot study, calls for population-based screening using capillary blood to identify cardiovascular features in the early stage, especially in populations with high familial burden (12). It also remains a concern in children, as evidenced by several case-to-control studies where family history was identified to predispose pediatric cancer patients to Anthracycline-induced cardiac diseases (13). Consequent health management of pure and off-pump CABG should also bear considerations of hereditary variation in vascular constriction and oxygenation (14).

Lastly, extensive observational studies involving tertiary care hospitals in India have also supported the correlation between FH and multivessel CAD in ACS patients and the severity and extent of lesions associated with FH of premature CVD (15). Collectively, these studies provide strong evidence that family history should not be seen as only a marker of pre-existing clinical risk but as an independent determinant of disease progression. From the summary of multiple centered works, it is crucial to embed the family history into diagnostic and prognostic paradigms. A well-designed observational study from Pakistan can significantly complement this narrative by quantitatively evaluating the relationship between a positive family history of premature CAD and angiographic severity of CAD. It is crucial to use such evidence for the formulation of screening protocols across geographically defined regions and propose a form of early detection of the corresponding risk, particularly in genetically vulnerable populations.

Objective

To determine whether a family history of premature coronary artery disease serves as an independent predictor of disease severity in patients diagnosed with CAD at a tertiary care hospital in Pakistan.

MATERIALS AND METHODS

Study Design: Observational, cross-sectional study.

Setting: This research was carried out at multi centers including Department of Cardiology, Ayub Teaching Hospital, Abbottabad and Hayatabad Medical Complex, Peshawar from June, 2023 to June, 2024.

Inclusion Criteria

Thus, the patients of the age group 30–60 years with documented CAD through angiographic evidence, presenting with stable angina, unstable angina, or acute MI angiographic evidence, were included. Patients who had coronary angiography during their hospital stay and had a documented family history of premature CAD (defined as CAD before 55 years of age in first-degree male relatives or 65 years of age in female first-degree relatives) were included.

Exclusion Criteria

Exclusion criteria included Congenital heart disease, Valvular heart disease, history of Coronary artery bypass grafting or stenting. Patients whose medical history was not appropriately documented or had uncertain family history were also excluded.

Methods

Participants selected in this study were patients aged between 30 and 60 years with any heart disease presenting in the cardiology inpatient and outpatient departments on a first-come, first-served basis. Demographic data, clinical history, and detailed family history of premature CAD were collected through structured questionnaires after explaining the study to the relatives and obtaining informed consent. Hematology, biochemistry, lipid profile, blood glucose, and renal profile were performed in all patients. In all the patients, diagnostic coronary angiography was done to evaluate the severity and the aggressiveness of CAD as single vessel disease, 2-vessel disease, or 3-vessel disease, respectively. Two operators determined the results of the coronary angiography with 5 years of experience in interventional cardiology who were unaware of the patient's family history. Thus, the degree of stenosis is evaluated through the Gensini scoring that estimates the luminal narrowing and the significance of the lesion's location. Data analysis used Statistic Package for the Social Science (SPSS) version 26. Chi-square and t-tests were conducted where appropriate the significance level was set at 0.05 to reveal the influence of family history on the severity of the disease.

RESULTS

In total, 320 patients with CAD were included in the trial. For example, 142 patients (44.4%) had documented FH of premature CAD, while the rest, 178 (55.6%), had no such history. The ages of the patients ranged between 42 and 69 years, and their mean age was 52.3 ± 7.6 years, with 68.7% of the patients being male. Among all the patients, 60.6% had hypertension, and 49.3% had diabetes mellitus. Patients who had a family history of coronary artery disease more often had acute coronary syndrome in comparison with those with no family history (64.8% vs 42.1%, p = 0.002). The results of the present revealed that smoking was seen more in patients who had no family history, while dyslipidemia was found more prominently in those who had a positive family history.

Table 1: Baseline Characteristics of Study Population

Parameter	Family History (+) (n=142)	Family History (−) (n=178)	p-value
Mean Age (years)	51.8 ± 7.2	52.7 ± 8.0	0.312
Male Gender (%)	70.4%	67.4%	0.591
Hypertension (%)	62.0%	59.5%	0.663
Diabetes Mellitus (%)	52.1%	46.6%	0.318
Smoking (%)	28.2%	40.4%	0.018
Dyslipidemia (%)	66.9%	49.4%	0.002
Acute Coronary Syndrome (%)	64.8%	42.1%	0.002

It was also noted that the extent of the disease was wider in patients having a family history, as seen from the data obtained through coronary angiography. Family history-positive patients had a higher incidence of triple-vessel disease and (TVD) = 39.4% as compared to 21.9% in the family history-negative patients. Single-vessel disease was more common in the non-familial group compared to the familial group.

Table 2: Extent of Coronary Artery Disease by Family History

Disease Severity	Family History (+) (n=142)	Family History (−) (n=178)	p-value
Single-Vessel Disease (SVD)	28.2%	44.9%	0.004
Double-Vessel Disease (DVD)	32.4%	33.2%	0.893
Triple-Vessel Disease (TVD)	39.4%	21.9%	0.001

Similarly, there were significant differences in scores for angiographic disease severity in the form of Gensini in patients with a positive family history. This study's mean score in this group was 74,2±18,6 as compared to 58,9 ± 16,3 in the other group (p <0,001).

Table 3: Comparison of Mean Gensini Score

Group	Mean Gensini Score ± SD	p-value
Family History (+) (n=142)	74.2 ± 18.6	<0.001
Family History (−) (n=178)	58.9 ± 16.3	

The results of the present study suggest that a history of premature CAD is a significant marker for the extent and severity of CAD.

DISCUSSION

This paper establishes a significant link between the inheritance factors of premature CAD and the extent of angiographically documented CAD in Pakistan. The patient group in this study had a documented family history of premature CAD at a rate of 44.4%, and this group had more extensive and more severe CAD with higher incidences of triple-vessel disease and higher Gensini scores. These results are consistent with prior research on family history as one of the modifiable risk factors yet having a significant impact on the clinical course and outcomes of cardiovascular disease. Several authors have underlined the importance of FH in the risk stratification of young patients with ACS. Higny & Dupont (1), in their observational study that employed the use of Cardiac CT, indicated that people who had a family history of premature CAD had increased subclinical atherosclerosis regardless of the absence of traditional risk factors. These are essential findings extending previous research by demonstrating that such patients not only manifest the disease at a younger age but also with higher angiographic severity, reflecting a genetic susceptibility to more advanced pathology.

Our study sample consisted of male participants with a mean age of 52.3 years, similar to several case series from South Asia (2). Sharma et al. (2) also highlighted similar age trends in CAD and significant reference to hereditary traits in the early onset of CAD in Indian patients, endorsing the regional significance of family history. Data regarding hypertension, diabetes, and smoking were similar in both groups, while dyslipidemia was higher in patients with positive family history, and more patients with acute coronary syndromes presented in a group with positive FH. This is similarly supported by the study by Sridevi et al. (4), which found it difficult to achieve the desirable lipid profile in CAD patients, particularly those with a first-degree relative. Because our research did not target pediatric or neonatal patients, the impact of genetic factors was also observed in early cardiovascular events. For instance, Zou et al. (3) discuss congenital cardiovascular risks in surgeries of infants. Similarly, Lin et al. (5) wrote about the perioperative EEG changes in children who underwent cardiac surgery. Several patients had a familial characteristic. This fact also contributes to the overarching idea of the lifelong involvement of genetic and familial factors in CVD.

Another study in the present context is Palla et al. (6) regarding cardiovascular risk in South Asian adults divided by metabolic syndrome status. They concluded that a family history should be included in the set of recommendations for screening, particularly in the area with a high risk for cardiovascular disease. The present study's findings can be used to supplement this recommendation, especially when the severity of the disease differs statistically significantly in patients with and without a family history. In addition, Cesaro et al. (7) previously studied the behavior of Lipoprotein(a) for individuals with premature acute coronary syndromes. The clinical significance of Lipoprotein(a), which is genetically determined, was established to have a direct relationship with the severity of CAD. This biological marker is thus postulated to have contributed to the increased disease burden recorded in this study among patients with family histories. However, the variable was not captured in this study. It is believed that the inclusion of such biomarkers in daily practice could positively contribute to early diagnosis in patient groups at particular risk.

However, the paper demonstrated that genetic factors are also relevant to other factors besides atherosclerosis. Forleo et al. (8) and Mohanty et al. (9) showed that these diseases have genetic components, mainly in the form of arrhythmic disorders and premature ventricular contractions. While these conditions differ from CAD, they exemplify other aspects of cardiovascular disease affected by family inheritance. Although these studies regarded arrhythmogenesis, they provide the basis for the general hypothesis of genetic stratum in cardiac disease. In addition, other vigorous observational studies, such as those in the CLASH study demonstrated by Schick et al. (10), suggest another crucial characteristic of prospective investigations is that recruited populations are well matched, which may help find other independent predictors like family history. In terms of the study, this approach is appropriate to our work and increases the level of internal validity of the study in terms of diagnostic and interventional measurements.

Family history could affect outcomes even among specific populations like women with peripartum cardiomyopathy (11). Companion-wise, Kiran et al. (11) indicated that markers of clinical and echocardiograms imparting poor prognosis were worse in individuals with a family history of cardiovascular diseases, suggesting that the family history should be incorporated into the risk assessment of various patient populations. As stated in the UNISCREEN project of Merolla and colleagues, universal screening programs are intended to identify people at risk for metabolic and cardiovascular diseases as soon as possible. They may not necessarily require interventional invasive investigations. In the present study, angiographic data were used to define the disease severity, while future studies can employ methods of screening biomarkers to identify the potential threats at the early stages of the disease.

It is supported by pediatric repercussions of hereditary cardiovascular risk factors, such as the study by Yu et al. (13) that established a higher risk of children to anthracycline-induced cardiotoxicity. On the same note, Han et al. (14) described how the genotype of vascular reactivity may have made individualized care that included tissue perfusion favorable for coronary artery bypass grafting patients. Taken together, the results emphasize that these chronic diseases should be considered a spectrum of cardiovascular risk determined by innate and socially acquired components. Last, Chowdhary et al. (15) conducted an observational study in a tertiary care hospital in India, and they observed a significantly higher incidence of multivessel CAD in a positive family history. This confirms our outcomes and provides further evidence for stating that family history is not only an additional factor but rather a determinant factor that influences the development of the disease.

CONCLUSION

This study at multi centers show that FH of CAD before the age of 55 years is an independent predictor of greater disease extent. The participants with a positive family history showed that they were more prone to triple-vessel disease, Gensini score, and acute coronary syndromes compared to the participants with a negative family history. The results suggest that family history should be an essential component of the standard cardiovascular screening process, especially in ethnic groups with a high prevalence of first-degree relatives with CVD, such as those originating from South Asian

countries. Understanding FH as an important non-genetic modifiable risk factor can facilitate clinicians in the early detection, risk assessment, and management of patients with a higher risk of suffering from severe CAD. Therefore, these findings underscore the importance of population-wide screening to involve first-degree relatives of patients with premature CAD, early lifestyle changes, and genetic testing to prevent the development of CAD in the next generation. Therefore, it is suggested that more extensive multiple-center studies be carried out to confirm the development of these findings.

REFERENCES

1- Higny, J. and Dupont, M., 2022. Cardiac CT findings in patients with family history of premature CAD: an observational study. Acta cardiologica, 77(7), pp.580-585.
2- Sharma, Y.P., Vemuri, K.S., Bootla, D., Kanabar, K., Pruthvi, C.R., Kaur, N., Nevali, K.P., Panda, P., Kasinadhuni, G., Uppal, L. and Mohanty, S., 2021. Epidemiological profile, management and outcomes of patients with acute coronary syndrome: multi centre experience from a tertiary care hospital in North India. Indian Heart Journal, 73(2), pp.174-179.
3- Zou, L., Yu, D., Wang, Q., Liu, H., Cun, Y., Li, Y., Qi, J., Mo, X., Peng, W. and Shu, Y., 2025. Timing of venoarterial extracorporeal membrane oxygenation in infant cardiac surgery: a multi-centre retrospective study of clinical outcomes. BMC Cardiovascular Disorders, 25(1), p.191.
4- Sridevi, C., Malani, S., Chaudhary, P.H., Nalawade, D.D., Shokeen, A., Sridevi, C., Chaudhary Sr, P.H., NALAWADE, D.D. and Shokeen Jr, A., 2024. Evaluation of Lipid Profile Management in Coronary Artery Disease Patients on Statin Therapy: A multi-Centre, Retrospective, Observational Study. Cureus, 16(10).
5- Lin, R., Du, N., Feng, J., Li, J., Li, L., Cui, Y., Ning, S., Zhang, M., Huang, G., Wang, H. and Zou, M., 2023. Perioperative EEG background and discharge abnormalities in children undergoing cardiac surgery: a prospective multi-centre observational study. British Journal of Anaesthesia, 131(2), pp.360-372.
6- Palla, A.H., Fatimi, A.S., Virani, S.S. and Fatima, S.S., 2023. Cardiovascular disease risk stratification in the Pakistani population with and without metabolic syndrome: A multi centre cross-sectional study. PLOS Global Public Health, 3(9), p.e0002397.
7- Cesaro, A., Acerbo, V., Scialla, F., Scherillo, G., De Michele, G., Panico, D., Porcelli, G., de Sio, V., Capolongo, A., Sperlongano, S. and Ruggiero, A., 2024. Role of LipoprotEin (a) in CardiovascuLar Diseases and Premature Acute Coronary Syndromes (RELACS Study): impact of Lipoprotein (a) levels on the premature coronary event and the severity of coronary artery disease. Nutrition, Metabolism and Cardiovascular Diseases, p.103843.
8- Forleo, C., Carella, M.C., Basile, P., Carulli, E., Dadamo, M.L., Amati, F., Loizzi, F., Sorrentino, S., Dentamaro, I., Dicorato, M.M. and Ricci, S., 2024. Missense and Non-Missense Lamin A/C Gene Mutations Are Similarly Associated with Major Arrhythmic Cardiac Events: A 20-Year multi-Centre Experience. Biomedicines, 12(6), p.1293.
9- Mohanty, S., Burkhardt, J.D., Di Biase, L., Mohanty, P., Shetty, S.S., Gianni, C., Della Rocca, D.G., Baho, K.K., Morris, T., Mayedo, A. and MacDonald, B., 2023. Best ablation strategy in patients with premature ventricular contractions with multiple morphology: a multi-centre experience. Europace, 25(5), p.euad038.
10- Schick, B., Barth, E., Mayer, B., Weber, C.L., Hagemeyer, T. and Schönfeldt-Lecuona, C., 2021. Prospective, observational, multi-centre cohort study with an independent control group matched for age and sex aimed at investigating the significance of cholinergic activity in patients with schizophrenia: study protocol of the CLASH-study. BMJ open, 11(12), p.e050501.
11- Kiran, G.R., RajKumar, C. and Chandrasekhar, P., 2021. Clinical and echocardiographic predictors of outcomes in patients with peripartum cardiomyopathy: a single centre, six month follow-up study. Indian Heart Journal, 73(3), pp.319-324.
12- Merolla, A., De Lorenzo, R., Ferrannini, G., Renzi, C., Ulivi, F., Bazzigaluppi, E., Lampasona, V. and Bosi, E., 2024. Universal screening for early detection of chronic autoimmune, metabolic

and cardiovascular diseases in the general population using capillary blood (UNISCREEN): low-risk interventional, single-centre, pilot study protocol. BMJ open, 14(3), p.e078983.

13- Yu, H., Qiu, Y., Yu, H., Wang, Z., Xu, J., Peng, Y., Wan, X., Wu, X., Jin, R. and Zhou, F., 2021. Anthracycline induced cardiac disorders in childhood acute lymphoblastic leukemia: a single-centre, retrospective, observational study. Frontiers in Pharmacology, 12, p.598708.

14- Han, J., Zhai, W., Wu, Z., Zhang, Z., Wang, T., Ren, M., Liu, Z., Sessler, D.I., Guo, Z. and Meng, L., 2025. Care guided by tissue oxygenation and haemodynamic monitoring in off-pump coronary artery bypass grafting (Bottomline-CS): assessor blind, single centre, randomised controlled trial. bmj, 388.

15- Chowdhary, G.S., Singh, A., Chowdhary, S., Gulati, R., Ahuja, M.S., Bhasin, A. and Padmini, H.S., 2025. An Observational Study of the Incidence and Risk Factors of Multivessel Coronary Artery Disease in Patients with Acute Coronary Syndrome Presenting at a Tertiary Care Hospital India. The Journal of the Association of Physicians of India, 73(1), pp.23-28.