Short Communication
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Overview of Pakistan Familial Hypercholesterolemia

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Abstract
Familial hypercholesterolemia (FH) is a genetic disease characterized by elevated low-density lipoprotein cholesterol (LDL-C), which leads to premature cardiovascular morbidity and mortality. This study provides details of the "Pakistan FH Registry" as a part of a global effort to harmonize the data and develop an effective management strategy for the disease. The four-year anonymized data (2018-2021) was obtained from the Shifa International Hospital, Islamabad database and regional collaborators in Pakistan. The patients were categorized based on Dutch Lipid Clinic Network criteria and entered into the registry. A total of 335 individuals were added to the registry, of which 165 were female (49.3%), and 170 (50.7%) were males. The median age at which the patients were diagnosed was 40 years (IQR= 26.5-53.0). Most patients (n=231) belonged to the possible FH category. The delayed diagnosis of FH can lead to premature cardiovascular morbidity and mortality. Dietary and lifestyle modifications are the first line of treatment for FH individuals. Earlier detection and effective nutrients and drug therapies could help reduce the global burden of FH.

***Keywords*:** Familial hypercholesterolemia, cardiovascular diseases, lipoprotein, registry

Highlight:

- The genetic disease of Familial hypercholesterolemia (FH)
- Elevation by low-density lipoprotein cholesterol (LDL-C),
- Pakistan FH Registry

1. Introduction

Familial hypercholesterolemia (FH) is a genetic disease that is characterized by the reduced clearance of low-density lipoprotein cholesterol (LDL-C) particles from the blood due to mutations in the genes for low-density lipoprotein receptor (LDLR), apolipoprotein B (APOB) or proprotein convertase subtilase/kexin type 9 (PCSK9) (Marks et al., 2003) This can result in premature cardiovascular morbidity and mortality due to atherosclerotic cardiovascular disease (ASCVD) (Migliara et al., 2017).

Severe atherosclerotic events occur during childhood among homozygous FH (HoFH) individuals (Tokgozoglu & Kayikcioglu, 2021). Clinical manifestations of FH include lipid deposits in the corneal arcus, xanthelasmas on eyelids and xanthomas on skin or tendons (McGowan et al., 2019). The diagnosis of FH can be determined based on available clinical criteria such as Dutch Lipid Clinic Network Diagnostic Criteria (DLCN), the Simon Broome Register Diagnostic Criteria, or the Make Early Diagnosis to Prevent Early Death (MEDPED) criteria. However, genetic screening provides insight into accurate molecular diagnosis, designing an effective lipid-lowering regimen and the stratification of cardiovascular risk (Medeiros & Bourbon, 2023).

In Pakistan, limited data on the prevalence and characteristics of FH is available. Being a multiracial country with a high rate of consanguineous marriages (63.6%). It is highly anticipated that the frequency of homozygosity for autosomal dominant traits, such as FH might be quite high in Pakistan (Albesher et al., 2022; Iqbal et al., 2022). A survey conducted in Pakistan among clinicians showed that a very small number of FH patients had been diagnosed. Moreover, lack of genetic testing, uniform diagnostic criteria and non-availability of resources are the major limitations for FH screening in the country (Sadiq et al., 2023).

Registries are effective tools to enhance knowledge dissemination and improve healthcare planning at the local level to tackle the global burden of FH (Hammond et al., 2013). Different registries have been initiated throughout the world that have helped identify new cases of FH as a result of cascade screening and referral to lipid clinics, and these have also helped to increase the knowledge of the physicians and healthcare professionals in terms of screening and diagnosis of the disease (Amerizadeh et al., 2022).

The European Atherosclerosis Society (EAS) Familial Hypercholesterolemia Studies Collaboration (FHSC) was created to establish a global registry for FH patients and to provide i) a platform to gather and harmonize data from all over the world, ii) to provide insights on the detection and management of FH, iii) that will help devise effective strategies to address the disease (Vallejo-Vaz et al., 2021) The initiative for Pakistan's first ever registry of FH patients named as "Pakistan FH Registry" was taken in November 2018 to contribute to the EAS FHSC. This study provides insights into Pakistan's contribution to the global registry.

2. Methods

The study was approved by Institutional Review Board and Ethics Committee (IRB&EC), Shifa Tameer-e-Millat University, Islamabad. The anonymized data on demographics, lipid profile and treatment regimen were obtained from the database of Shifa International Hospital, Islamabad, spanning four years (2018-2021). Moreover, some of the patients were added based on clinical diagnoses by our regional collaborators. The participants were selected based on clinical presentation and Dutch Lipid Network Criteria (DLCN) evaluation. The individuals were grouped into categories; Definite, Probable, Possible and Unlikely FH based on DLCN criteria. The data of the individuals with definite, probable FH and possible FH were entered into FH Pakistan registry, which feeds into the FHSC global registry through a secure server.

2.1 Statistical analyses

The data were organized in Microsoft Excel for further analysis. Categorical variables, such as the number of individuals, were presented as frequencies and percentages, while continuous variables, such as age, were presented as median and Interquartile range (IQR).

3. Results

The records of 335 individuals were added to the registry. Among these, 165 were female (49.3%), while 170 were male (50.7%). With regards to age categories, 26 (7.8%) were aged less than 10 years, 36 (10.7%) were aged between 10 to 20 years, 41 (12.2%) between 21 to 30 years, 68 (20.3%) between 31 to 40 years, 66 (19.7%) between 41 to 50 years while 97 (29%) were older than 50 years. The median age of participants at entry into the registry was 40 years (IQR= 26.5-53). Among the identified individuals, 73 (21.7%) belonged to the definite FH category, while 31 (9.2%) belonged to the probable FH category, and 231 (68.9%) belonged to the possible FH category.

4. Discussion

FH is an autosomal inherited disease that is characterized by elevated LDL-C levels. Those with heterozygous FH (HeFH) commonly have untreated cholesterol levels between 250 and 300 mg/dL (6.5-7.8 mmol/L), which can result in cardiovascular events by the ages of 30 to 50 years for males and 40 to 60 years for women (Tokgozoglu & Kayikcioglu, 2021). The prevalence of FH in the general population is estimated to be 1:313 individuals. At the same time, it is 10 times greater in people with ischemic heart disease (IHD), 20 times higher in people with premature IHD, and 23 times higher in people with severe hypercholesterolemia. In contrast, the prevalence is unknown in 90% of the countries(Beheshti et al., 2020). Despite being declared a public health priority by World Health Organization (WHO) and with more than 25 million cases reported worldwide, there is no consensus on the detection and screening strategies (Vallejo-Vaz et al., 2021). Moreover, global disparities in the availability of existing lipid lowering treatments, control of LDL-C levels and genetic testing remain an ongoing challenge in managing FH (Tromp et al., 2022).

Dietary and lifestyle modifications are the first line of treatment for FH individuals; however, multidrug treatments are a requisite for significantly lowering LDL-C levels (McGowan et al., 2019). Statin therapy, particularly a maximum tolerated dose of high-potency statins, remain the first and most widely used treatment for FH patients and can significantly lower LDL-C levels (McGowan et al., 2019). Dual therapy with Ezetmibe statin significantly lowers the mean LDL-C levels. Other treatment options include PCSK9 inhibitors, mipomersen, lomitapide, and bempedoic acid; however, these drugs are associated with high cost and unavailable globally (McGowan et al., 2019) (Tromp et al., 2022). LDL apheresis involves the physical removal of lipoprotein from blood and could be effective in lowering LD-C levels, however, their availability and cost remain an unresolved issue (Raal et al., 2018).

FH registries can serve as a platform for gathering and examining information about FH patients, which can aid in identifying areas for improvement and healthcare gaps. Moreover, these can aid fundamental research by offering high-quality, anonymized aggregate data and can enable geographically equitable access to clinical trials (Evans et al., 2013) (Hammond et al., 2013). The EAS FHSC studies collaboration is a network comprising investigators from 75 countries worldwide. The present study provided insights into the contribution of Pakistan to the global FH registry. The results of the present study indicate that a considerably smaller number of FH patients have been entered into FH Pakistan registry, despite the expected higher prevalence of FH in Pakistan.

Moreover, the diagnosis was made late in life (above 40 years), showing the delayed diagnosis of FH. The global perspective of the FHSC registry also showed the same results, where more than half of the adults were diagnosed above 40 years while only 2% were diagnosed before the age of 18 (Vallejo-Vaz et al., 2021). These findings imply that the diagnoses and ultimate therapeutic interventions for FH occur too late, increasing the risk of premature cardiac events and mortality. Table (1) shows an overview of the conducted studies on the characteristics of FH patients

Table 1: Overview of studies conducted worldwide reporting characteristics of FH patients

	Present study	(Vallejo-Vaz et al., 2021)	(Tromp et al., 2022)	(Alhabib et al., 2021)	(Degoma et al., 2016)	(Mehta et al., 2021)	(Brunham et al., 2018)
Country	Pakistan	Global	Global	Gulf	USA	Mexico	Canada
Number of participants	335	42 167	751	3713	1295	336	3122
Male	170	19031	362	1765	526	222	3097
Female	165	21999	389	1948	769	114	25
Median diagnosis age (years)	40	46.2	12*	49	47	50	43

* only homozygous FH patients are included in the study

4.1 Limitations

The number of participants in the registry was considerably low since the data for this study was obtained predominantly from Islamabad. This study does not provide a complete picture of the prevalence or situation of FH in Pakistan. The network needs to be strengthened further to identify more FH patients from the entire country and register with the FH Pakistan registry.

5. Conclusion

Familial hypercholesterolemia is diagnosed late, and hence the treatment goals remain unachieved. Therefore, to improve familial hypercholesterolemia care globally, early, systematic detection of the condition and increased use of combination medication are required.

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Conflict of Interest: No conflict of interest between the Authors

References

Albesher, N., Massadeh, S., Hassan, S. M., & Alaamery, M. (2022). Consanguinity and Congenital Heart Disease Susceptibility: Insights into Rare Genetic Variations in Saudi Arabia. *Genes 2022, Vol. 13, Page 354*, *13*(2), 354.

Amerizadeh, A., Javanmard, S. H., Sarrafzadegan, N., & Vaseghi, G. (2022). Familial Hypercholesterolemia (FH) Registry Worldwide: A Systematic Review. *Current Problems in Cardiology*, *47*(10), 100999.

Alhabib, K. F., Al-Rasadi, K., Almigbal, T. H., Batais, M. A., Al-Zakwani, I., Al-Allaf, F. A., Al-Waili, K., Zadjali, F., Alghamdi, M., Alnouri, F., Awan, Z., Kinsara, A. J., AlQudaimi, A., Almahmeed, W., Sabbour, H., Traina, M., Atallah, B., Al-Jarallah, M., AlSarraf, A., … Altaradi, H. (2021). Familial Hypercholesterolemia in the Arabian Gulf Region: Clinical results of the Gulf FH Registry. *PLOS ONE*, *16*(6)

Beheshti, S. O., Madsen, C. M., Varbo, A., & Nordestgaard, B. G. (2020). Worldwide Prevalence of Familial Hypercholesterolemia: Meta-Analyses of 11 Million Subjects. *Journal of the American College of Cardiology*, *75*(20), 2553–2566.

Brunham, L. R., Ruel, I., Khoury, E., Hegele, R. A., Couture, P., Bergeron, J., Baass, A., Dufour, R., Francis, G. A., Cermakova, L., Mancini, G. B. J., Brophy, J. M., Brisson, D., Gaudet, D., & Genest, J. (2018). Familial hypercholesterolemia in Canada: Initial results from the FH Canada national registry. *Atherosclerosis*, *277*, 419–424

Degoma, E. M., Ahmad, Z. S., O'Brien, E. C., Kindt, I., Shrader, P., Newman, C. B., Pokharel, Y., Baum, S. J., Hemphill, L. C., Hudgins, L. C., Ahmed, C. D., Gidding, S. S., Duffy, D., Neal, W., Wilemon, K., Roe, M. T., Rader, D. J., Ballantyne, C. M., Linton, M. F., … Knowles, J. W. (2016). Treatment Gaps in Adults With Heterozygous Familial Hypercholesterolemia in the United States: Data From the CASCADE-FH Registry. *Circulation. Cardiovascular Genetics*, *9*(3), 240–249

Evans, S. M., Loff, B., & Cameron, P. A. (2013). Clinical registries: the urgent need to address ethical hurdles. *The Medical Journal of Australia*, *198*(3), 134–135.

Hammond, E., Watts, G. F., Rubinstein, Y., Farid, W., Livingston, M., Knowles, J. W., Lochmüller, H., Bellgard, M., & Dawkins, H. J. (2013). Role of international registries in enhancing the care of familial hypercholesterolaemia. *International Journal of Evidence-Based Healthcare*, *11*(2), 134–139.

Iqbal, S., Zakar, R., Fischer, F., & Zakar, M. Z. (2022). Consanguineous marriages and their association with women's reproductive health and fertility behavior in Pakistan: secondary data analysis from Demographic and Health Surveys, 1990–2018. *BMC Women's Health*, *22*(1), 1–16.

Marks, D., Thorogood, M., Neil, H. A. W., & Humphries, S. E. (2003). A review on the diagnosis, natural history, and treatment of familial hypercholesterolaemia. *Atherosclerosis*, *168*(1), 1–14.

McGowan, M. P., Hosseini Dehkordi, S. H., Moriarty, P. M., & Duell, P. B. (2019). Diagnosis and treatment of heterozygous familial hypercholesterolemia. *Journal of the American Heart Association*, *8*(24).

Medeiros, A. M., & Bourbon, M. (2023). Genetic Testing in Familial Hypercholesterolemia: Is It for Everyone? *Current Atherosclerosis Reports*, *25*(4), 127.

Mehta, R., Martagon, A. J., Galan Ramirez, G. A., Antonio-Villa, N. E., Vargas-Vázquez, A., Elias-Lopez, D., Gonzalez-Retana, G., Rodríguez-Encinas, B., Ceballos-Macías, J. J., Romero-Zazueta, A., Martinez-Alvarado, R., Morales-Portano, J. D., Alvarez-Lopez, H., Sauque-Reyna, L., Gomez-Herrera, L. G., Simental-Mendia, L. E., Garcia-Aguilar, H., Ramirez-Cooremans, E., Peña-Aparicio, B., … Aguilar-Salinas, C. A. (2021). Familial hypercholesterolemia in Mexico: Initial insights from the national registry. *Journal of Clinical Lipidology*, *15*(1), 124–133

Migliara, G., Baccolini, V., Rosso, A., D'Andrea, E., Massimi, A., Villari, P., & de Vito, C. (2017). Familial Hypercholesterolemia: A Systematic Review of Guidelines on Genetic Testing and Patient Management. *Frontiers in Public Health*, *5*, 252.

Raal, F. J., Hovingh, G. K., & Catapano, A. L. (2018). Familial hypercholesterolemia treatments: Guidelines and new therapies. *Atherosclerosis*, *277*, 483–492.

Sadiq, F., Shafi, S., Sikonja, J., Khan, M., Ain, Q., Khan, M. I., Rehman, H., Mlinaric, M., Gidding, S. S., Groselj, U., Alam, J., Ali, M., Anwer, J., Awan, W. A., Bham, S. Q., Fatima, N., Gul, F., Hameed, S. S., Haroon, M., Zehra, T. (2023). Mapping of familial hypercholesterolemia and dyslipidemias basic management infrastructure in Pakistan: a cross-sectional study. *The Lancet Regional Health - Southeast Asia*, *0*(0), 100163.

Tokgozoglu, L., & Kayikcioglu, M. (2021). Familial Hypercholesterolemia: Global Burden and Approaches. *Current Cardiology Reports*, *23*(10), 1–13.

Tromp, T. R., Hartgers, M. L., Hovingh, G. K., Vallejo-Vaz, A. J., Ray, K. K., Soran, H., Freiberger, T., Bertolini, S., Harada-Shiba, M., Blom, D. J., Raal, F. J., Cuchel, M., Tromp, T. R., Hartgers, M. L., Hovingh, G. K., Vallejo-Vaz, A. J., Ray, K. K., Bertolini, S. A., Pang, J., Raal, F. J. (2022). Worldwide experience of homozygous familial hypercholesterolaemia: retrospective cohort study. *The Lancet*, *399*(10326), 719–728.

Vallejo-Vaz, A. J., Stevens, C. A. T., Lyons, A. R. M., Dharmayat, K. I., Freiberger, T., Hovingh, G. K., Mata, P., Raal, F. J., Santos, R. D., Soran, H., Watts, G. F., Abifadel, M., Aguilar-Salinas, C. A., Alhabib, K. F., Alkhnifsawi, M., Almahmeed, W., Alnouri, F., Alonso, R., Al-Rasadi, K., Ray, K. K. (2021). Global perspective of familial hypercholesterolaemia: a cross-sectional study from the EAS Familial Hypercholesterolaemia Studies Collaboration (FHSC). *The Lancet*, *398*(10312), 1713–1725.

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