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Original Research

Early mortality in children with homozygous familial hypercholesterolemia: Case reports of deaths at ages 5 and 7 and a systematic review of global evidence

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KEYWORDS
Familial hypercholesterolemia;
Homozygous FH;
Mortality;
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LDLR

BACKGROUND: Homozygous familial hypercholesterolemia (HoFH) is a leading cause of premature atherosclerotic cardiovascular disease (ASCVD) and early mortality if left untreated or inadequately treated.

OBJECTIVE: This study presents 2 pediatric cases of early death from Pakistan due to familial hypercholesterolemia (FH) and provides a systematic review of similar cases reported globally.

METHODS: Genetic analysis was conducted using next-generation sequencing to confirm pathogenic variants. For the systematic review, published reports of individuals with FH who died before the age of 18 years were identified. Data were extracted on demographic features, personal and family history, genetic variants, treatment given, and cause of death.

RESULTS: Both patients, born to consanguineous families, presented with markedly elevated low-density lipoprotein cholesterol (LDL-C) levels (792 mg/dL [20.48 mmol/L] and 896 mg/dL [23 mmol/L], respectively), multiple xanthomas, and early-onset myocardial infarction, and died at the ages of 5 and 7 years, respectively. Their genetic analysis revealed a pathogenic frameshift variant in the *LDLR* gene: NM_000527.5: c.2416dupG (p.Val806GlyfsTer11). The systematic review included 12 studies reporting pediatric FH-related mortality. Common clinical features included tendon xanthomas,

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elevated LDL-C levels, family history, and early-onset ASCVD. Genetic testing was performed in a few cases, which revealed pathogenic variations in the *LDLR* gene. Most of the patients received inadequate lipid-lowering therapy. The most common causes of death were severe coronary artery disease, myocardial infarction, and sudden cardiac arrest.

CONCLUSION: Our 2 cases and the accompanying systematic review identified additional cases of premature mortality. Collectively, these findings highlight diagnostic delays and inadequate treatment as common factors among patients who died prematurely.

Introduction

Familial hypercholesterolemia (FH) is an autosomal codominant disorder characterized by reduced clearance of low-density lipoprotein cholesterol (LDL-C) particles from the blood and is the major risk factor for atherosclerotic cardiovascular disease (ASCVD).[1] Although heterozygous FH (HeFH) affects approximately 1 in 313 people globally, it remains underdiagnosed, with fewer than 10% of cases identified, while > 80% of those receiving treatment fail to reach the recommended lipid-lowering targets.[2,3]

As the traits in FH are inherited in an autosomal codominant pattern, 2 disease-causing variants can be inherited by an individual, clinically resulting in homozygous FH (HoFH). It is a rare form of FH characterized by extremely elevated LDL-C levels, often exceeding 13 mmol/L, with an estimated prevalence of 1 in 300,000 individuals.[4] A high number of individuals with HoFH remain undiagnosed, misdiagnosed, and/or receive a late diagnosis, often after a major cardiovascular event.[5] Despite treatment with multiple lipid-lowering therapies, most patients do not reach the treatment goals.[6] Evidence suggests that the majority of individuals with HoFH die before the age of 40, often after experiencing recurrent ASCVD events.[7,8] The burden is particularly severe in low- and middle-income countries, where timely diagnosis and access to effective treatment remain major challenges.[7,8]

The estimated combined prevalence of HeFH in Pakistan is 1:273 individuals; however, the diagnosis and hence the treatment remain delayed.[9,10] Guideline-recommended practices such as genetic testing and cascade screening are rarely performed.[11,12] This diagnostic delay is particularly devastating in children with HoFH, for whom early identification and aggressive lipid-lowering therapy are critical to survival.[13] In Pakistan, the combination of high consanguinity rates and low awareness further increases the risk of severe, undetected HeFH and particularly HoFH cases.[10]

Despite the high risk of cardiovascular complications in children with HoFH, the literature contains a limited number of documented cases of FH-related pediatric mortality. To date, no systematic review has been conducted to comprehensively analyze the clinical profiles, genetic testing, treatment histories, and other factors associated with premature deaths. Furthermore, there is a lack of structured identification of key barriers such as diagnostic delays, inadequate access to lipid-lowering therapies, and limited use of genetic testing, which may have contributed to these outcomes. In this article, we describe 2 cases of HoFH in Pakistani children who died due to premature cardiovascular events before the age of 8. In addition, we conducted a systematic review of the literature to systematically collect and summarize clinical data on individuals with FH who died from cardiovascular causes during childhood or adolescence (under 18 years of age), representing the highest-risk subgroup within the FH population.

Patients and methods

Patients

We conducted a retrospective evaluation of medical records from 2 unrelated pediatric patients who died due to FH-related complications identified through the Lipid Clinic Network, Pakistan. Both patients were referred to the clinics at the age of 3 and 5, respectively, due to markedly elevated LDL-C levels and the presence of multiple xanthomas. The diagnosis of FH was confirmed through genetic testing in each case. Both patients experienced an early-onset cardiovascular event and died before the age of 8.

Informed consent was taken from the guardians/caregivers of the patients, and their clinical and family histories were obtained. CAse REport (CARE) and Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA) reporting guidelines were used for case report presentation and a systematic review.

Genetic testing

Genomic DNA was extracted from the venous blood using the QIAMP DNA kit (Qiagen). Genetic analysis was conducted following a previously established protocol at the University Children's Hospital, Ljubljana, Slovenia.[14]

The coding regions and intron-exon borders of the dyslipidemia-related genes were sequenced through xGen Lockdown next generation sequencing (NGS) Probes using the MiSeq Reagent Kit (Illumina). The genes included in the analysis were *ABCA1, ABCG5, ABCG8, ALMS1, APOA1, APOA5, APOB,*

APOC2, APOC3, APOE, CREB3L3, GPIHBP1, LDLR, LDLRAP1, LIPA, LMF1, LPL, and *PCSK9*. Variant classification followed American College of Medical Genetics and Genomics (ACMG) standards and guidelines for the interpretation of variants.[15] The validation of the pathogenic variants was performed by Sanger sequencing.

Systematic review

A comprehensive search until April 25, 2025, was conducted on 3 databases: PubMed, Web of Science, and Google Scholar. A manual search of reference lists from included articles was also conducted. The search was conducted using a combination of keywords "familial hypercholesterolemia", "FH", "homozygous FH", "pediatric FH", "mortality", and "childhood". According to the inclusion criteria, studies conducted on the pediatric population (< 18 years) with a confirmed diagnosis of FH, either clinical or genetic, including case reports, case series, cohort studies, cross-sectional studies, and clinical trials, studies on humans, and studies published in English were included. Studies reporting adult FH or those without clear evidence of early mortality and review articles were excluded. Moreover, all studies were included regardless of their publication date.

The screening of titles and abstracts of all identified studies was carried out by 2 reviewers. After the initial screening, the full texts of the potentially eligible studies were assessed against the inclusion and exclusion criteria. In case of any disagreements, a discussion or consultation with a third reviewer was taken. Data were extracted using a standardized form, including study characteristics (author, year, country, study design), demographics (age, biological sex as reported in clinical records or publications, family history), FH details (diagnosis, either clinical or genetic), treatment received, and cause and age of death, by 2 independent reviewers.

The systematic review identified a total of 1950 studies through database searches in PubMed, Web of Science, and Google Scholar. After removing duplicates, 1686 studies remained for title screening. Following this initial screening, 100 studies were eligible for abstract screening, and among these, 30 studies underwent full-text review. Ultimately, 8 studies met the inclusion criteria and were included in the final analysis. The reference list of the selected articles was screened to identify more studies, and 3 studies were added in the final review. In total, 12 studies were included in the final analysis. The PRISMA flow diagram detailing the study selection process is presented in the Figure.

Results

Case series

Patient 1 was a 5-year-old girl from a family in Punjab, Pakistan, where multiple generations had consanguineous marriages.[11] She presented with multiple tendinous and planar xanthomas, including interdigital planar xanthomas, and had an extremely elevated untreated LDL-C level of 792 mg/dL (20.48 mmol/L), along with a lipoprotein(a) concentration of 182 mg/dL. Her clinical history included a myocardial infarction (MI) occurring at the age of 3, followed by coronary artery bypass graft surgery. She was treated with high-intensity lipid-lowering therapy, including rosuvastatin (40 mg once daily), ezetimibe (10 mg once daily), and cholestyramine (4 g once daily) from the age of 3. Genetic testing identified a homozygous pathogenic frameshift variant in the *LDLR* gene: NM_000527.5: c.2416dupG (p.Val806GlyfsTer11). Both parents were confirmed heterozygous carriers of the same variant, with LDL-C levels of 163 mg/dL (4.21 mmol/L) and 333 mg/dL (8.61 mmol/L), respectively. Despite treatment, she suffered another MI and died at the age of 5.

Patient 2 was a 7-year-old boy from a consanguineous family in Punjab, Pakistan. At the age of 5, he presented with the classical clinical features of FH, including tendinous xanthomas, corneal arcus, and an extremely elevated LDL-C level of 896 mg/dL (23 mmol/L). Echocardiography revealed features suggestive of supravalvular aortic stenosis, mild aortic regurgitation, mild mitral regurgitation, and left venticular (LV) dysfunction. At the age of 6, he was initially treated with rosuvastatin 10 mg once daily for approximately 1 year. A few weeks before his death, the dose was increased to 20 mg, and ezetimibe (10 mg once daily) and cholestyramine (4 g once daily) were added to his regimen. At the age of 7, he suffered an MI, was subsequently hospitalized, and passed away 10 days later. Genetic analysis revealed a homozygous pathogenic frameshift variant in the *LDLR* gene: NM_000527.5: c.2416dupG (p.Val806GlyfsTer11), with both parents confirmed as heterozygous carriers. The LDL-C levels of the parents were 288 mg/dL (7.44 mmol/L) and 325 mg/dL (8.40 mmol/L), respectively.

Systematic review

The details of the studies included in the final review, which reported cases of children diagnosed with FH, either clinically or genetically, who died before the age of 18, are given in the Table. The majority of studies were case reports or small case series that reported 12 cases of pediatric mortality due to FH-related complications. The age at death ranged from 2 to 14 years.[16,17] Males constituted approximately 11/14 (78.5%) of the cases. All patients were reported as having HoFH and exhibited classical clinical features such as multiple xanthomas and elevated LDL-C levels (typically > 300 mg/dL). A positive family history for premature cardiovascular disease (CVD) was noted in several cases, where the information was documented. One patient was diagnosed posthumously.[18] Genetic confirmation was available in only 4 cases, identifying variants in the *LDLR* gene.[18–21] None of the reported cases had variants in *APOB* or *PCSK9* genes. Parental consanguinity was

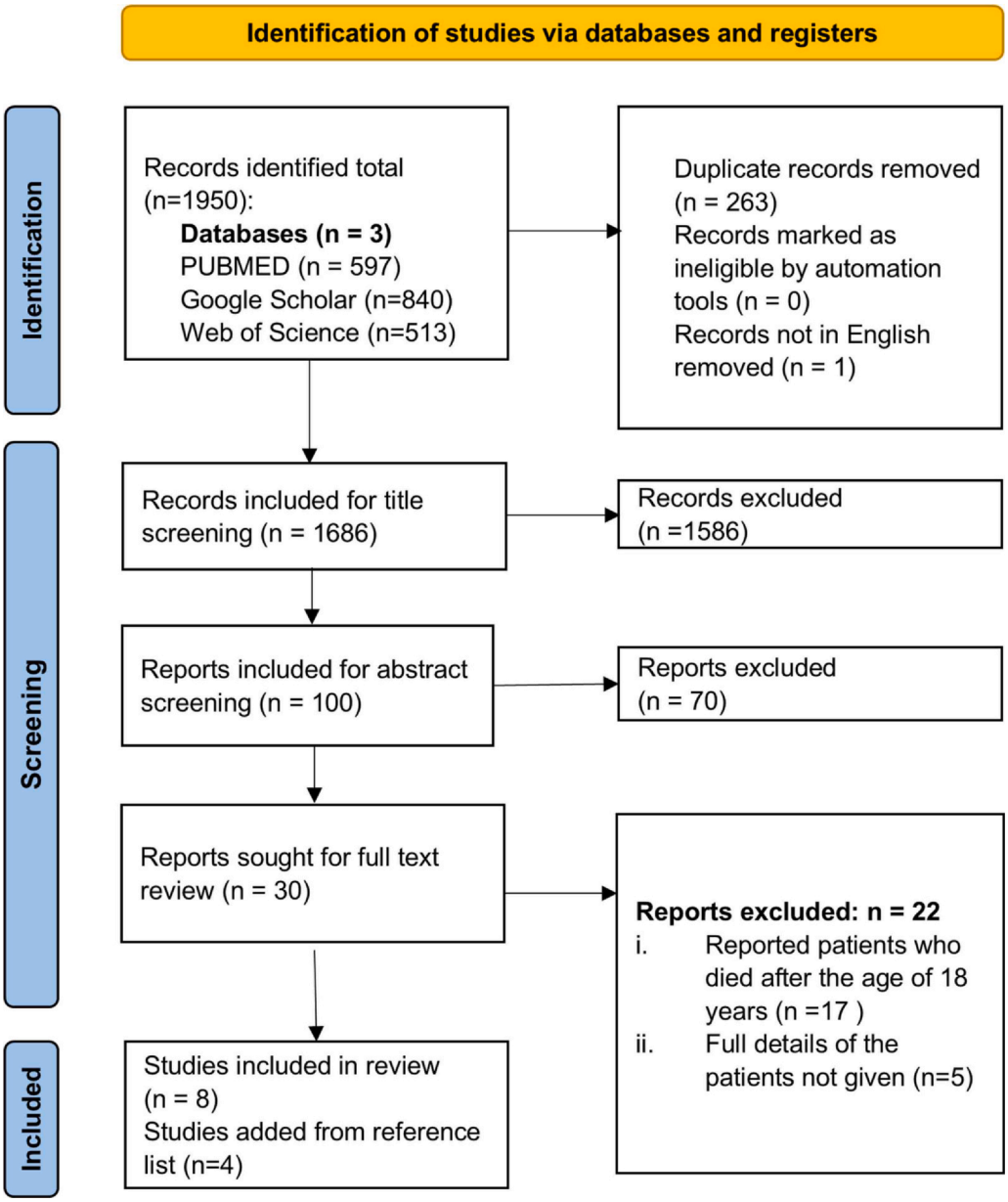

Figure PRISMA flowchart with the number of records identified, screened, assessed for eligibility, and included in the final analysis. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

reported in a few cases, while this information was unavailable for several other cases.[17,18,20] CVD complications were common, with reported events including aortic stenosis, angina pectoris, MI, coronary artery disease, myocardial ischemia, and cardiomyopathy. The leading causes of death were severe coronary artery disease, MI, and sudden cardiac arrest, sometimes during or after physical exertion. Among the included cases, very few children received guideline-recommended therapies, and most were either untreated or inadequately treated. Lipid-lowering therapy, when administered, typically involved statins with or without ezetimibe.[20–22] Diagnostic delays were observed for most of the cases, with many cases being diagnosed only after the onset of serious cardiac complications or even after death.

Discussion

This study presents 2 cases of early mortality in children with FH from Pakistan and provides a systematic review of published cases with similar outcomes globally. Both the children presented with the hallmark features of HoFH, including multiple xanthomas, markedly elevated LDL-C levels, and premature CVD events. The systematic review of literature with similar cases also revealed comparable findings, particularly in cases where diagnosis was delayed or treatment was suboptimal. A large study from 20 countries reported the median age of death among patients with HoFH to be 37 years, while the median age of diagnosis for these patients was 12 years.[6] Furthermore, a meta-analysis of 94 studies reported the prevalence of MI

Table Clinical and genetic characteristics of patients in the present study and cases of pediatric mortality associated with familial hypercholesterolemia included in the systematic review.

ID	Ethnicity/ Country	Dx age	Tx start age	Death age	Sex	Xanth-oma	LDL-C[a] (mg/dL)	TC[a] (mg/dL)	HDL-C[a] (mg/dL)	Treatment	Variant	Family history	Consanguinity	CVD event	Cause of death	Reference
1	Punjabi/ Pakistan (present study)	3 y	3 y	5 y	♀	+	792	829	25	Rosuvastatin 40 mg, Ezetimibe 10 mg, cholestyramine 4 g	*LDLR* NM_000527.5:c.2416dupG (p.Val806GlyfsTer11)	+	+	MI	MI	-
2	Punjabi/ Pakistan (present study)	5 y	6 y	7 y	♂	+	896	944	24	Rosuvastatin 10 mg	*LDLR* NM_000527.5:c.2416dupG (p.Val806GlyfsTer11)	+	+	AS	MI	-
3	Japanese/ Japan	11 y	NA	11 y	♂	+	NA	908	NA	NA	NA	NA	No	AS	Heart failure	[42]
4	Canadian/ Canada	22 mo	22 mo	2 y	♂	+	845	948	28	Low-fat diet, cholestyramine 0.7/kg/d	NA	+	No	NA	Coronary death	[16]
5	French-Canadian/ Canada	9 y	NA	11 y	♀	+	NA	1050	NA	Portacaval shunt	NA	NA	NA	Angina, MI	NA	[43]
6	NA/ Australia	NA	NA	10 y	♂	+	707	1106	8	Nil	NA	+	No	MI	MI	[44]
7	French/ Canada	1.8 y	NA	3.1 y	♂	+	928	950	28	Low-fat diet, cholestyramine, niacin, or lovastatin[b,c]	*LDLR* (NM_000527.5): c.1055G > A (p.Cys352Tyr)	NA	NA	Coronary artery occlusion	Sudden cardiac death	[19]
8	Indian/ India	14 y	NA	14 y	♂	+	345	442	60	Nil	NA	NA	Yes	CAD	Sudden death	[17]
9	Turkish/ Austria	2 y	3 y	4 y	♂	+	800	833	31	Atorvastatin, ezetimibe[b]	*LDLR* (NM_000527.5): c.1666T > C (p.Trp556Arg)	NA	NA	AS	Sudden cardiac death	[21]
10	Turkish/ Turkey	NA[d]	NA	13 y	♀	+	647	885	35	NA	NA	NA	NA	AS	Postoperative respiratory insufficiency	[45]
11	Turkish/ Switzerland	NA	3.5 y	4.5 y	♂	+	NA	1124	27	Dietary control, atorvastatin (5 mg)	*LDLR* (NM_000527.5):c.1849delA (p.Val597Tyrfs45X)	+	Yes	MI	MI	[20]

(*continued on next page*)

Table (*Continued*)

ID	Ethnicity/ Country	Dx age	Tx start age	Death age	Sex	Xanthoma	LDL-C[a] (mg/dL)	TC[a] (mg/dL)	HDL-C[a] (mg/dL)	Treatment	Variant	Family history	Consanguinity	CVD event	Cause of death	Reference
12	Indian/ India	9 y	9 y	10 y	♂	+	363	379	NA	Atorvastatin[b]	NA	NA	NA	Cardiomyopathy	Cardiac failure	22
13	NA/ Italy	1 y	1 y	5 y	♀	+	1005	NA	NA	Colestyramine, LDL apheresis[b]	NA	NA	NA	Left Coronary obstruction	MI	46
14	Syrian/ Germany	After death	NA	2 y 11 mo	♂	+	NA	NA	NA	Nil	*LDLR* (NM_000527.5): c.1222G > A) p.Glu408Lys	+	Yes	AS	Sudden cardiac death	18

Abbreviations: ♂, male; ♀, female; AS, aortic stenosis; CAD, coronary artery disease; CVD, cardiovascular disease; Dx, diagnosis; HDL-C, high-density lipoprotein cholesterol; LDLR, low-density lipoprotein receptor; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; NA, not available; TC, total cholesterol; Tx, treatment.

[a]Baseline measurement.

[b]Exact dose not mentioned.

[c]Exact drug not mentioned.

[d]Diagnosed after death.

among patients with HoFH to be 15.1%, with an average onset age of 24.5 years and a coronary revascularization prevalence of 28.3% with an average onset age of 32.2 years. Post-1990 cohorts demonstrated a delayed onset of major adverse cardiovascular events, likely reflecting improved survival due to advances in lipid-lowering therapies.[23]

Delayed or missed diagnosis is one of the most important challenges in FH care. It has been estimated that < 5% cases of HoFH are diagnosed globally.[2,24] The systematic review also identified instances where patients were either diagnosed after death or only identified among the siblings following the death of a child, suggesting that the condition may have gone unrecognized in earlier cases within the family.[18] This pattern was also observed in other studies from Pakistan, where new FH diagnoses in families were only made following the sudden death of a child.[11,25] These delays in diagnosis could be due to inadequate awareness among physicians and the public, lack of universal screening practice, and low prioritization of FH in healthcare policies.[26] Screening strategies such as universal screening in childhood and cascade screening of family members have proven effective in early identification of FH cases, enabling timely intervention and potentially preventing premature cardiovascular events.[27–29] Besides these, other innovative approaches—such as opportunistic screening; involvement of non-primary care health professionals, such as pharmacists and optometrists; point-of-care cholesterol testing; and incorporation of FH variants into newborn or population-wide genetic screening programs—have also been proposed.[30]

Genetic testing not only provides a definitive molecular diagnosis but also is effective in the initiation and adherence of lipid-lowering therapy and, consequently, significant LDL-C reduction among patients with FH.[31] Among the cases identified through the systematic review, genetic testing was performed only in 4 cases, but most of the cases were reported before genetic testing was commonly recommended for FH. In both our reported cases and those identified through the systematic review, all pathogenic variants were found in the *LDLR* gene. *LDLR*-related pathogenic variants account for 85% to 90% of all identified variants of FH, reinforcing the role of this gene in disease pathogenesis.[32] Individuals carrying *LDLR* null/null variants typically experience more aggressive disease progression and have been reported to die well before the median age of death reported.[8] While current guidelines recommend aggressive LDL-C–lowering therapies, including high-dose statins, ezetimibe, and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, these therapies are often ineffective in patients with complete loss-of-function variants.[7] In that case, LDLR-independent therapies, such as lomitapide, evinacumab, and mipomersen, are more effective, enabling patients with HoFH to achieve their LDL-C goals.[33,34] The systematic review highlights that most individuals did not receive the guideline-recommended treatment, likely due to limited therapeutic options at the time or because the studies were

conducted before the current treatment protocols were established. Therefore, the early mortality observed in these patients likely results from the nonavailability of advanced lipid-lowering therapy. In Pakistan, statins and ezetimibe are the only available treatment options. Advanced treatment options such as PCSK9 inhibitors and lipid and plasma apheresis are not available, resulting in poor management of FH.[10]

In most cases included in this study, the primary causes of death were cardiovascular in nature, including coronary artery disease, MI, and sudden cardiac arrest, often occurring during or after physical activity. These fatal events reflect the aggressive and early onset of atherosclerotic disease in individuals with HoFH, often developing in early childhood. Clinical or subclinical manifestations of atherosclerosis, including aortic stenosis, coronary artery disease, and myocardial ischemia, were commonly observed before death. The use of imaging techniques such as echocardiography, coronary artery calcium (CAC) score, and coronary angiography can be particularly useful in detecting subclinical atherosclerosis in patients with FH, resulting in a timely diagnosis and management in both patients with HeFH and those with HoFH.[35–37] Recent recommendations by the European Society of Cardiology and European Atherosclerosis Society also endorse the use of imaging modalities such as CAC scoring as risk modifiers, particularly in individuals with moderate risk or near treatment thresholds.[38]

Limitations

One of the major limitations of the study is that the number of cases included was very low. Since most of the studies were case reports or case series, the data might be incomplete or biased. There was considerable heterogeneity in the levels of details given in the studies included, particularly with respect to lipid profiles and treatment given, making direct comparison difficult. Since we included only those studies that were in English, we might have missed cases published in other languages. Some studies reporting FH-related deaths were excluded from the review due to insufficient clinical details, such as missing biochemical profiles or family history data.[39–41] For our cases, post-treatment data were incomplete, preventing the assessment of treatment response.

Conclusion

This study highlights the severe clinical outcomes and early mortality associated with HoFH, as demonstrated by the 2 cases from Pakistan and those identified through a systematic review. A key contribution of this work is the synthesis of clinical characteristics common among children and adolescents who died early, including extremely elevated LDL-C levels, the presence of xanthomas, a positive family history of CVD, and delayed and inadequate treatment. These findings may help clinicians recognize high-risk pediatric patients with FH, resulting in prompt diagnosis and initiation of intensive lipid-lowering therapy. The findings of this study also emphasize the need to increase awareness among physicians and patients, promote universal and cascade screening for early identification of FH, and ensure equitable access to lipid-lowering therapies and imaging tools for timely detection and management of FH. Further studies on early deaths in children with FH are needed to better understand the underlying risk factors and to assess the impact of timely diagnosis and intervention strategies, particularly in middle- and low-income countries.

CRediT authorship contribution statement

Madeeha Khan: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis. **Quratul Ain:** Writing – review & editing, Investigation, Formal analysis. **Jaka Sikonja:** Writing – review & editing, Supervision. **Barbara Cugalj Kern:** Writing – review & editing, Validation, Methodology, Investigation. **Hijab Batool:** Writing – review & editing, Resources. **Sabeen Abid Khan:** Writing – review & editing, Resources. **Muhammad Qasim Hayat:** Writing – review & editing, Supervision. **Mohammad Iqbal Khan:** Writing – review & editing, Resources. **Urh Groselj:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization. **Fouzia Sadiq:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

Ethical approval

The study was approved by the Institutional Review Board and Ethics Committee of Shifa Tameer-e-Millat University, Islamabad, Pakistan (033-523-2019) and National University of Sciences and Technology (2025-IRB-A-80/80).

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, AI has not been used in the writing process.

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bodies had no role in and were not involved in the study design, data collection, management, analysis and interpretation, manuscript preparation, or the decision to submit the manuscript for publication.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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