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Premature Sudden Cardiac Death as a Diagnostic Indicator for Familial Hypercholesterolemia

Dr Murooj Fadlelmula[1]*, Dr Mohamed Babiker Elhag[1]

[1]Family Medicine Consultant PHCC-Qatar

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***Corresponding author:** Dr Murooj Fadlelmula
Family Medicine Consultant PHCC-Qatar

Abstract **Review Article**

Familial hypercholesterolemia remains significantly underdiagnosed despite its severe impact on cardiovascular morbidity (Gidding *et al*., 2024; Knowles *et al*., 2014). Elevating premature sudden cardiac death as a sentinel diagnostic criterion is essential for identifying affected asymptomatic individuals before lethal events occur. It ensures early implementation of lipid-lowering therapies that effectively mitigating the progression of preventable atherosclerotic cardiovascular disease (Campbell-Salome *et al*., 2021; Watts *et al*., 2023). Furthermore, leveraging this indicator helps overcome the limitations of current diagnostic models, which often fail to account for the diverse genetic modifiers and polygenic factors that influence phenotypic expression (Fahed & Nemer, 2011). Given that individuals with familial hypercholesterolemia experience an increased risk of atherosclerotic cardiovascular disease up to ten-fold compared to the general population, utilizing fatal cardiac events as a diagnostic trigger can dramatically improve case detection (Knowles *et al*., 2017). (Trinder *et al*., 2020). Moreover, adopting this mortality-centric diagnostic trigger aligns with contemporary efforts to integrate automated electronic health record querying, which can facilitate active case-finding across large patient populations (Ahmad *et al*., 2016; Gu *et al*., 2024). Such data-driven identification models, particularly when utilizing electronic healthcare records, have demonstrated superior cost-effectiveness and efficacy compared to universal population screening, offering a scalable solution to reach national detection targets (Page *et al*., 2023a, 2023b).

Keywords: Familial hypercholesterolemia, sudden cardiac death, coronary atherosclerosis, lipid metabolism, diagnostic criteria, genetic testing.

INTRODUCTION

Familial hypercholesterolemia is a prevalent autosomal dominant disorder characterized by lifelong exposure to elevated low-density lipoprotein cholesterol, which significantly elevates the risk of premature atherosclerotic cardiovascular disease (Community *et al.,* 2020).

Pathophysiological Mechanisms

Persistent hypercholesterolemia facilitates the infiltration and sequestration of low-density lipoproteins within the coronary artery intima, where they undergo oxidative modification and promote the development of fibroatheromatous plaques (Harada-Shiba *et al.,* 2018).

Lipid Metabolism Impairment

The condition is fundamentally driven by a critical deficiency in the LDL receptor pathway, which impairs the hepatic clearance of circulating cholesterol and results in its prolonged residence time within the bloodstream (Boutgourine et al., 2024; Yamagishi et al., 2021). This molecular defect, primarily stemming from mutations in the *LDLR* gene, prevents the necessary endocytosis of apolipoprotein B-containing particles (Rasheed et al., 2024; Yu *et al.,* 2022). Consequently, the resulting systemic elevation in plasma LDL-C levels accelerates the progression of coronary atherosclerosis (Cao *et al., 2018; Marco-Benedí et al., 2022)*. In young adults, these unstable plaques can trigger fatal arrhythmias through acute myocardial infarction or ischemia-induced electrical instability, often serving as the primary manifestation of undiagnosed familial hypercholesterolemia (Larsen *et al.,* 2012; Risgaard *et al.,* 2013). The acute physiological stress induced by these ischemic events, coupled with the underlying structural vascular pathology, lowers the ventricular fibrillation threshold, culminating in sudden cardiac death (Votýpka *et al.,* 2023).

Arrhythmic Risk Factors

Current Diagnostic Frameworks the Dutch Lipid Clinic Network criteria rely heavily on LDL-C thresholds and family history, yet these scoring systems often overlook the critical prognostic significance of premature sudden cardiac death in first-degree relatives.

Standard Clinical Criteria

Current diagnostic paradigms remain heavily anchored in lipid profile assessment and standardized pedigrees, which frequently fail to capture asymptomatic cases that present initially as fatal cardiac events (Mach *et al.,* 2019; Mytilinaiou *et al.,* 2018).

Cardiac Death Clinical Significance

Integrating premature sudden cardiac death as a definitive diagnostic marker, rather than a mere secondary observation, provides a more aggressive pathway for identifying high-risk kindreds (Yao *et al.,* 2021).

Methodological ImplementationA retrospective analysis of autopsy findings must be systematically conducted to correlate myocardial histopathology with specific molecular genotypes identified in SCD cohorts.

Retrospective analysis of autopsy findings in young victims of sudden cardiac death often reveals advanced coronary atherosclerosis and elevated lipid profiles consistent with underlying familial hypercholesterolemia, even in the absence of previous clinical symptoms (Kunutsor *et al.,* 2016).

Data Synthesis Approaches Integrating this mortality data requires embedding autopsy-derived evidence directly into existing diagnostic algorithms, thereby elevating sudden cardiac death as an independent criterion for family screening.

Integrating mortality data into diagnostic algorithms necessitates the systematic aggregation of post-mortem coronary histopathology, enabling clinicians to reclassify previously idiopathic cases of sudden death as index events for hereditary lipid disorders (Banderali et al., 2022; Cuchel *et al.,* 2014).

Future Clinical Implications

To mitigate these outcomes, healthcare systems must mandate systematic, family-based cascade screening for every sudden cardiac death survivor or victim, transitioning from passive screening to active clinical outreach (Lin et al., 2023). Moreover, national health policies should be overhauled to incentivize universal lipid testing at birth or early childhood, ensuring that genetic predispositions are identified well before the manifestation of lethal ischemic events (Cohen & Stefanutti, 2021; Dharmayat *et al.,* 2023). By establishing clinical pathways that trigger mandatory lipid evaluation for the biological relatives of any individual who suffers a premature cardiac arrest, clinicians can unveil occult hereditary conditions and initiate tailored prevention strategies (Rajan et al., 2025; Sen-Chowdhry & McKenna, 2006).

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