SHORT COMMUNICATION

USE OF POLYGENIC AND CLINICAL RISK SCORES IN WIDE SPECTRUM CONGENITAL HEART MALFORMATIONS: A DIAGNOSTIC AND THERAPEUTIC PERSPECTIVE

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Worldwide, congenital heart defects (CHDs) are a leading cause of mortality and morbidity. Globally, the annual prevalence rate of CHDs is about 1.5 million. It is one of the most common life-threatening congenital malformations, with a visible difference between high-income countries (HICs) and developing countries. This difference may be attributed to the diagnostic facilities and interventions.[1] Moreover, the use of genetic and clinical risk scores is less studied in this field compared to other diagnostic and therapeutic approaches. Thus, we comprehensively review the available literature on adult and pediatric syndromic or non-syndromic CHDs and propose limitations and future directions in this field. Risk factors for this fatal disease include genetic and environmental factors.[2,3] Risk stratification based on prenatal diagnosis with genetic counseling has shown better clinical outcomes. The modified World Health Organization (mWHO) guidelines are among the first proposed for risk stratification based on clinical scores.[4] The combination of polygenic risk scores (PRS) and clinical risk evaluation has been adopted in various populations as better diagnostic and therapeutic approaches for various diseases, including coronary artery disease,[5] diabetes,[6] obesity,[7] and cancers.[8,9] However, unlike these diseases, polygenic risk scores are rarely used for the genetic diagnosis of CHD patients. The clinical utility of polygenic risk scores for CHDs is still in the early stages and requires validation studies in different cohorts. Incorporating PRS into the clinical setting may improve CHD diagnosis and therapeutic strategies.[10] Recently, an initial attempt was made to determine the clinical utility of polygenic risk scores in a large dataset of the European cohort. Data from this study suggested a high potential for PRS in distinguishing between clinical phenotypes (mild, moderate, and severe) of congenital heart malformations.[11] Furthermore, this hypothesis was tested in patients with transposition of the great arteries (TGA) to assess the utility of risk stratification after arterial switch operation. The cumulative risk score was computed for single nucleotide polymorphisms (SNPs) that reached the threshold statistical significance of $p<1\times10^{-5}$ in the initial analysis. Combined clinical and polygenic risk scores showed improved risk stratification in mild, moderate, and severe TGA phenotypes.[12] Similarly, in another European cohort, the risk allele frequency was higher in the diseased group compared to the control group. However, statistical analysis suggested a non-significant association with $p>0.05$. Interestingly, combined risk scores constructed for selected SNPs showed a significant association with the disease with a p-value of 0.002. This evidence further supports the hypothesis that the cumulative effect of polymorphisms has better diagnostic and therapeutic efficacy than individual SNPs.[13] There are certain limitations to its clinical use. Firstly, social stigma and lack of awareness regarding this disease are major hurdles. Secondly, there is a need to recruit a large number of samples from different populations to validate the clinical utility of PRS. Additionally, a lack of resources in developing countries also contributes to fatal outcomes. We recommend conducting large cohort studies in different ethnic groups to predict better risk associations, develop better therapeutic strategies, and formulate management guidelines.

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AUTHORS' CONTRIBUTION

SA, KA, and AUR: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work

Disclaimer: None.

Conflict of interest: Authors declared no conflict of interest.

Source of funding: None.

Double blinded peer review history:
Submission complete: November 10, 2023
Review began: November 13, 2023
Revision received: December 1, 2023
Revision accepted: December 8, 2023

Citation: Ashiq S, Ashiq K, Rehman AU. Use of polygenic and clinical risk scores in wide spectrum congenital heart malformations: a diagnostic and therapeutic perspective. Pak Heart J. 2024;57(01):75-76. DOI: https://doi.org/10.47144/phj.v57i1.2670

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