Review Article

Role of Vascular Endothelial Growth Factor as a Potential Biomarker in Congenital Heart Defects: A Systematic Review

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Abstract

Background: *Several studies have investigated the role of vascular endothelial growth factor (VEGF) variants, serum levels, and correlations with other extrinsic factors in congenital heart defects (CHDs); however, the findings need confirmation. The present systematic review evaluates the association between CHDs and genetic polymorphisms and serum expressions.*

Methods: *Relevant literature was searched through electronic databases using keywords and MeSH terms. VEGF activity was comparatively assessed between cyanotic and acyanotic CHDs, and the association between different polymorphisms and heart defects was evaluated.*

Results: *We ultimately evaluated 12 studies regarding the association between VEGF serum patterns and found that serum VEGF levels were upregulated or downregulated in correlation with hypoxia and hemoglobin levels and were significantly associated with cyanotic CHDs compared with acyanotic CHDs. Our results also showed a significant role for different single-nucleotide polymorphisms, including rs699947, rs2010963, and rs3025039.*

Conclusion: *The findings of the current study suggested a significant association between CHDs and VEGF genetic polymorphisms or varied serum levels. Nevertheless, more comprehensive studies may provide conclusive results and valuable insights into the pathogenesis of CHDs and relevant treatment strategies.*

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Keywords: *Heart defects, congenital; Polymorphism, genetic; Vascular endothelial growth factors*

Introduction

Congenital heart defects (CHDs) are the most common birth defects that arise in the heart and its associated vessels during cardiac embryogenesis.[1] Moreover, CHDs can increase the risk of heart disease even after surgical treatment or in the later life of the patient.[2] Approximately 80% of cases remain uncertain, but 20% of heart defects are due to genetic factors, maternal diabetes, or teratogen exposure.[3] CHDs occur in approximately 1% of births

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and rank first in birth-related infant mortality. In addition, children with complex CHDs are more at risk for other disease-related morbidities.[4] Worldwide, the incidence of CHDs ranges from 4 to 5 per thousand live births, while it affects approximately 40,000 births in Pakistan and the United States annually.[5] Overall, the prevalence of CHDS was reported highest in the Asian population and lowest in the African region. The reasons for the difference in prevalence may include genetic and environmental factors, including maternal illnesses and age-related factors.[6]

The clinical assessment of patients encompasses 3 evaluation strategies: physical examinations, cardiac lesion classifications, and pedigree or genetic evaluations.[7] Broadly, CHDs can be divided into 2 major categories: cyanotic and acyanotic.[8] CHDs are subdivided into isolated or complex defects that occur in other heart defects or are associated with the syndromic condition.[9] The oxygen saturation (SPO_2) level is above 95% in acyanotic heart diseases such as septal defects, while levels are below 95% in cyanotic heart defects such as transposition of the great arteries and tetralogy of Fallot.[10] Pulse oximetry, in combination with physical examination, increases the specificity and sensitivity of CHD screening; nonetheless, a negative screening test does not exclude the possibility of heart defects. The most common clinical symptoms include breathing difficulty, feeding difficulty, and failure to thrive, while signs include tachycardia, murmurs, and desaturation.[11]

The etiology of CHDs is complex and multifactorial; it involves genetics, epigenetics, and environmental factors. Although genetic factors constitute the principal contributor to disease development, approximately 80% of genetic mechanisms have remained poorly understood.[12] One of the key players in CHD pathogenesis is the vascular endothelial-derived growth factor (*VEGF*). This gene is involved in both angiogenesis and vasculogenesis. Enhanced *VEGF* expression levels can stunt angiogenesis and contribute to disease development; still, some investigations have reported that various cardiac defects occur due to mutations that cause decreased *VEGF* activity or loss of function.[13] Five key members of this gene are *VEGF-C* and *VEGF-D*, which play an essential role during lymphangiogenesis. Similarly, the placental growth factor, *VEGF-A*, and *VEGF-B* modulate angiogenesis. The *VEGF-A* gene contains 7 introns and 8 exons and is present on chromosome 6p21.1.[14] Moreover, the mentioned gene is crucial during cardiac septal and valve formation by upregulating the mesenchymal transformation, whereas in the atrioventricular field of the heart tube, it downregulates the endocardial-to-mesenchymal transformation.[15] The evidence further suggests that several functional single-nucleotide polymorphisms (SNPs) also regulate *VEGF* production.[16] Many studies have reported a significant association between the 5′-UTR polymorphism (rs2010963) and 2 key promoter polymorphisms (rs699947 and rs1570360) and *VEGF* secretion and conotruncal septal defects like tetralogy of Fallot.[17] In addition, *VEGF* expression is also regulated by environmental conditions, such as hypoxia, which is further supported by animal studies and found to be associated with cardiac malformations such as outflow tract and atrioventricular canal obstruction in mice.[18] Thus, in the current study, we focus on the association between CHDs and SNPs in the *VEGF* gene, the role of serum *VEGF* levels, and their relationship with SPO_2.

The relationship reported between SNPs in the *VEGF* gene and CHDs remains inconsistent in different populations, including Asians and Caucasians. Additionally, the serum *VEGF* pattern and its association with various blood indices and polymorphisms need clarification. Accordingly, we designed the present systematic review to elucidate the association between variants in the *VEGF* gene and CHDs and variations in serum levels related to SPO_2 and hemoglobin levels, which may provide better insights into the pathophysiology of the diseases underlying CHDs. Through this systematic review, we aimed to determine the association between reported SNPs and CHDs. This study also evaluates the serum *VEGF* patterns and their relationship with SPO_2 and hemoglobin levels in cyanotic and acyanotic CHDs.

Methods

The current study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2009 (PRISMA 2009). The study was also registered with PROSPERO (PROSPERO registration number: CRD42021288429). The PRISMA checklist is also provided as a supplementary file. All the relevant literature published between 2000 and 2023 was retrieved by using Cochrane Library, Web of Science (WOS), Scopus, MEDLINE, Ovid, and EMBASE through the following keywords and MeSH terms: ‘CHD’, ‘vascular endothelial growth factor’, ‘congenital heart diseases’, ‘*VEGF*’, ‘single nucleotide polymorphism’, ‘genotype’, ‘mutation’, and ‘worldwide’. The duplicates were removed, and a manual literature search was performed to avoid missing any potential study. The articles were selected when the following requirements were met: 1) full-length original articles investigating the association between *VEGF* levels and CHDs, 2) studies investigating the role of most common SNPs in CHDs, and 3) studies providing adequate information for the comparison of *VEGF* concentrations between cyanotic and acyanotic CHDs. Articles with insufficient information, systematic reviews, and articles written in languages other than English were excluded from the final analysis. The publication selection

bias was decreased by using predesigned data extraction tables. Each author independently reviewed and extracted the required information from the final selected studies. The following information was extracted from each study: authors' names, country, publication year, sample size, *VEGF* concentrations, most common SNPs, *VEGF* serum measuring method, and SPO_2 and hemoglobin levels. The detailed characteristics are presented in Tables 1, 2, and 3. The Newcastle-Ottawa Scale (NOS) score was used to evaluate the quality of each original article. The range for this scoring system was from 0 to 9. Each author independently assessed the quality of the individual study, and any disagreements were resolved through discussion. The comparative analysis of *VEGF* serum levels between cyanotic and acyanotic CHDs was visualized with bar

Table 1. Association between VEGF serum levels and CHDs reported in different studies

Author	Year	Country	Sample Size			Age			Sex			Method	VEGF Serum Levels (pg/mL)			Effects on CHDs (P value)
			Cases		Control	Cases		Control	Case M/F		Control		Cases		Control	
			C	AC		C	AC		C	AC			C	AC		
Baghdady et al	2010	Egypt	35	30	-	3.10±1.60	3.00±1.70	-	-	-	-	ELISA	150.30±48.10	85.40±18.70	-	<0.001
El-Melegy et al	2010	Egypt	30	30	25	3.38±0.78	3.20±2.12	3.48±2.31	16/14	22/8	15/10	VEGF165 ELISA	410.83±102.79	308.66±85.74	141.40±55.38	<0.001
Liu et al	2009	China	15	15	-	-	-	-	-	-	-	ELISA	201.42±44.74	113.56±35.62	-	<0.050
Hu et al	2005	China	22	24	-	7.80±7.70	9.70±10.20	-	T=25/21	-	-	ELISA	946.30±371.40	289.00±32.20	-	<0.001
Ootaki et al	2003	Japan	61	102	-	6.00±3.40	-	-	-	-	-	Quantikine VEGF ELISA Kit	355.00±287.10	203.00±221.60	-	<0.001
Himeno et al	2003	Japan	80	-	81	4.20	-	4.80	36/44	-	43/38	Quantikine VEGF ELISA Kit	149.20±105.60	-	66.30±22.50	<0.001
Starnes et al	2000	United States of America	22	19	-	1.60	12.20	-	11/11	10/9	-	Quantikine VEGF ELISA Kit	129.60	<129.60	-	0.030
Zhang et al	2009	China	20	48	20	-	-	-	-	-	-	-	171.70±54.80	125.90±35.40	33.20±11.70	<0.010 CHD vs C <0.010 C vs AC
Suda et al	2004	Japan	24	19	-	8.70±6.50	8.90±4.90	-	-	-	-	ELISA	443	180	-	<0.010
Nassef et al	2014	Egypt	60	60	30	1.00:4.00	1.00:4.00	1.00:4.00	26/34	35/25	50%/50%	ELISA	192.66±5.50	180.66±4.0415	167.73±2.5334	<0.050
Steurer et al	2017	United States of America	93	-	194	-	-	-	-	-	-	Milliplex Map kit	4.55±1.93	-	4.29±1.99	0.300
Sochet et al	2020	United States of America	37	27	-	-	-	-	-	-	-	ELISA Quantikine Kits	127.50	64	-	0.030

VEGF, Vascular endothelial growth factor; CHDs, Congenital heart defects; C, Cyanotic; AC, Acyanotic; C, Controls; M, Male; F, Female; ELISA, Enzyme-linked immunosorbent assay

Table 2. Association between systemic room air oxygen saturation and hemoglobin levels

Author	Year	Air Oxygen Saturation (%)			P value	Hemoglobin (g/dL)			P value
		Cases		Control		Cases		Control	
		C	AC			C	AC		
Baghdady et al	2010	80.40±2.40	97.50±1.90	-	<0.001	13.50±1.70	11.81±0.97	-	<0.001
El-Melegy et al	2010	80.60±7.30	97.10±0.50	-	<0.001	16.70±2.50	10.00±2.10	-	<0.001
Liu et al	2009	-	-	-	-	-	-	-	-
Hu et al	2005	84.20±7.30	97.30±1.70	-	<0.001	18.80±2.50	10.00±2.10	-	<0.001
Ootaki et al	2003	80.40±9.50	98.70±1.80	-	<0.001	-	-	-	-
Himeno et al	2003	80.60 ± 7.30	___	98.10± 0.50	<0.001	-	-	-	-
Starnes et al	2000	79.80±7.70	99.50±1.00	-	<0.001	-	-	-	-
Zhang et al	2009	80.50±2.90	-	NR	<0.010	15.01±1.42	-	NR	<0.010
Suda et al	2004	76.90± 8.70	97.70± 0.70	-	<0.010	-	-	-	-
Nassef et al	2014	-	-	-	-	-	-	-	-
Steurer et al	2017	-	-	-	-	-	-	-	-
Sochet et al	2020	-	-	-	-	-	-	-	-

C, Cyanotic; AC, Acyanotic; C, Controls; NR, Normal range

Table 3. Baseline characteristics, genotyping, and NOS scores of the included SNP studies

Author	Year	Country	Sex-Wise Distribution		Mean Age	SOC	Sample Size		Genotyping	SNPs Studied		NOS Score
			Cases (M/F)	Controls (M/F)			Cases	Controls		Significant	Nonsignificant	
Li et al	2015	China	103 / 57	148 / 92	4.27±1.93	HB	160	240	PCR-RFLP	rs699947 rs2010963 rs3025039	-	8
Wang et al	2014	China	160 / 84	84 / 52	1.58±1.61 (controls) 1.55±1.70 2.27±4.49 (cases)	HB	244	136	MALDI-TOF-MS	-	rs699947 rs833061 rs2010963 rs3025039	8
Yan et al	2015	China	108 / 57	148 / 92	1.55±0.79 (cases) 1.57±0.73 (controls)	HB	165	240	MassARRAY	rs699947 rs3025039 rs1570360	rs833061 rs25648 rs833068 rs3020040 rs10434	8
Calderon et al	2009	Chile	28/33	26/35	3.90±5.30 (cases) 8.60±9.40 (controls)	HB	61	61	PCR-RFLP Capillary sequencing	-	rs699947 rs1570360 rs2010963	8
Sallmon et al	2019	Germany	271 / 249	236 / 297	26.70 (cases) 30 (controls)	HB	520	533	PCR-RFLP Sequencing	-	rs2010963	8
Smedts et al	2010	Netherlands	96 / 94	170 / 147	16.20 (cases) 16.10 (controls)	HB	190	317	TaqMan allelic discrimination assay	-	rs699947 rs1570360 rs2010963	8
Xie et al	2007	China	167 / 55	-	-	HB	222	352	PCR-RFLP	-	rs699947 rs1570360 rs2010963	7
Ashiq et al	2023	Pakistan	68 / 41	65 / 35	5.45 (cases) /4.07 (controls)	HB/ PB	225	151	Minisequencing	-	rs833061 rs1570360	8
Ding et al	2016	China	54 / 46	53 / 47	3 (cases) 3 (controls)	HB	476	557	PCR-RFLP	-	rs699947 rs833061 rs2010963 rs3025039	8

SOC, Source of controls; NOS, The Newcastle-Ottawa Scale; PCR, Polymerase chain reaction; RFLP, Restriction fragment length polymorphism; MALDI-TOF-MS, Matrix-assisted laser desorption/ionization-time of flight mass spectrometry; M, Male; F, Female

graphs. This analysis was performed using Microsoft Excel.

Results

After applying our inclusion criteria and comprehensive literature screening, we identified 240 relevant original studies, of which 228 articles were not included in the final analysis. The complete screening method is described in Figure 1. Three studies involved Chinese, American, Egyptian, and Japanese populations.

The variable concentrations of *vascular endothelial growth factors* were reported in different studies (Table 1). In addition, the associations between *VEGF* and hemoglobin and systemic room air SPO_2 levels were also observed. The levels of SPO_2 and hemoglobin also showed significant variations between cyanotic and acyanotic CHDs (Table 2).[19-30] All the included studies showed a significant association between *VEGF* levels and CHDs. *VEGF* concentrations also differed between cyanotic and acyanotic CHDs (Figure 2).

The most common genetic polymorphisms reported concerning the *VEGF* gene are rs699947, rs833061, rs2010963, rs3025039, rs25648, rs833068, rs3020040, rs10434, and rs1570360. These SNPs showed a significant role in susceptibility to CHDs in different populations.[17,18,31-37] Table 3 describes the genotyping techniques used in various ethnic groups and SNPs associated with CHDs. The NOS scores of these included studies ranged from 7 to 8.

Discussion

Several studies have investigated the role of *VEGF* in CHDs, but the present study is a comprehensive analysis of the relationship between CHDs and *VEGF* polymorphisms and serum *VEGF* levels and includes comparative assessments between cyanotic and acyanotic CHDs. We also provide information vis-à-vis *VEGF* and its relationship with hemoglobin and systemic room air SPO_2. The *VEGF* gene plays a crucial role due to its potential role in vasculogenesis and angiogenesis; thus, an SNP may disrupt its activity and contribute to disease development.[38] However, other factors, including hypoxia, can further worsen the disease outcomes.

The results of our systematic review suggested a potential

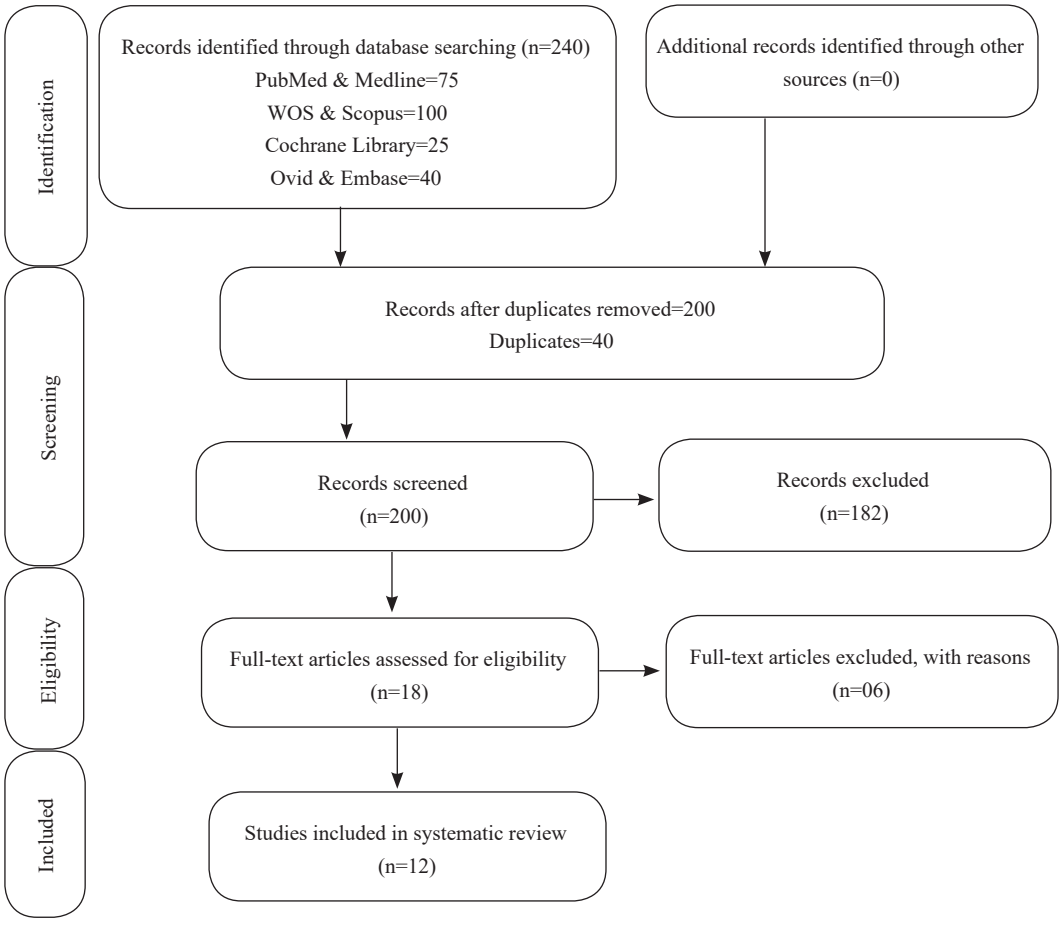

Figure 1. The image depicts the flow diagram of study selection.

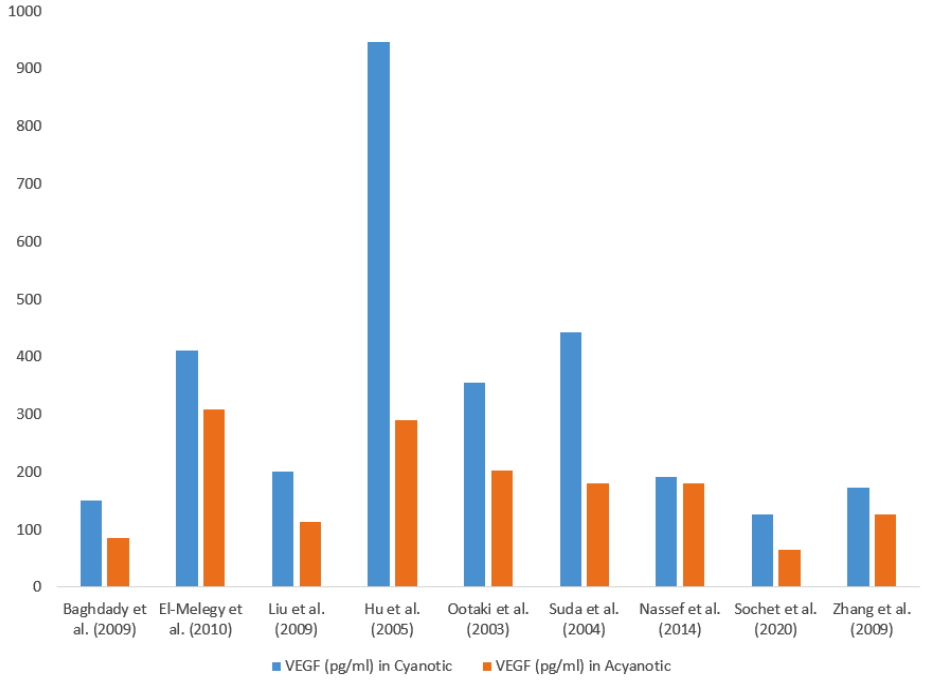

Figure 2. The image compares serum VEGF levels between cyanotic and acyanotic congenital heart diseases.
VEGF, Vascular endothelial growth factor

role for the *VEGF* gene variants in patients with CHDs. Furthermore, we found a more significant association between cyanotic CHDs and low SPO_2 or hemoglobin levels. Our findings chime with those reported by Hamada et al[39] and Yin et al.[40] Likewise, a prior investigation reported a significant association between CHDs and SNPs, including rs3025039, rs833061, and rs1570360.[41] In contrast, a nonsignificant association was found between CHDs and *VEGF* +936C>T, −2578C>A, −634G>C, and −1498T>C polymorphisms in the Chinese population.[32] In Italian patients with CHDs, a nonsignificant role for the rs3025039 variant was suggested.[42] Similarly, in a hospital-based study, Ding et al[37] reported a nonsignificant impact for 4 polymorphisms, namely T+936, C-2578, G-634, and T-1498. The reported variations in the roles of SNPs may stem from ethnic variations or environmental factors.

Our systematic review also provides a comprehensive assessment of the VEGF gene and its activity in CHDs. Be that as it may, our results should be interpreted in light of some limitations. Firstly, we conducted a systematic review of a large number of variants but did not perform a pooled analysis due to variations in the data reported. Secondly, we selected only the literature published in the English language, which may contribute to publication bias.

Conclusion

Based on the results of the present systematic review, the *VEGF* gene polymorphisms are significantly associated with CHDs, and their expression levels are also regulated by other factors, including hypoxia and hemoglobin levels. We recommend further comprehensive research to gain better insights into the pathophysiology of the diseases underlying CHDs, including the roles of genetic variants and serum activity.

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