Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://doi.org/10.21608/zumj.2025.359414.3837 Volume 31, Issue 6 June. 2025
Manuscript ID:ZUMJ-2502-3837
DOI:10.21608/zumj.2025.359414.3837

Original Article

Plasma Haptoglobin Level as a Diagnostic Biomarker in Children with Ventricular Septal Defect

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Submit Date09 -02-2025
Revise Date17 -02-2025
Accept Date19 -02-2025

ABSTRACT

Background: Ventricular septal defect (VSD) is the most common congenital cardiac defect, occurring in 30–60% of all neonates with congenital cardiovascular abnormalities. Haptoglobin is an acute-phase protein with antibacterial and antioxidant properties. The current study aimed to explore the value of haptoglobin in the diagnosis of VSD.

Methods: This study was performed at the Pediatric Cardiology Unit of Zagazig University Children's Hospital on 72 children. Thirty-six children had VSD with or without Heart failure. Thirty-six children were healthy. Heart failure was classified according to the Modified Ross classification. Echocardiography was performed, and plasma haptoglobin levels were measured in all participants.

Results: Plasma haptoglobin level was reduced in VSD patients compared with controls (p-value less than 0.001). Haptoglobin level was less in patients with VSD and heart failure compared with the control group (p-value less than 0.001). There was a substantial inverse association between plasma haptoglobin and heart failure grades (r = -0.644, p-value less than 0.001). The optimal haptoglobin cutoff for diagnosing VSD was ≤8.045 mg/dL, with an area under the curve (AUC) of 0.864, sensitivity of 80.6%, and specificity of 94.4%.

Conclusion: Haptoglobin levels were consumed in VSD cases. A negative correlation was found between haptoglobin and the severity of heart failure. Haptoglobin plasma level was 80.6 % sensitive and 94.4% specific in the diagnosis of VSD.

Keywords: Ventricular Septal Defect; Haptoglobin; Heart Failure

INTRODUCTION

Congenital cardiac defects have a birth incidence of 9.1 per 1000 live births. The VSDs account for 30–60% of all newborns with congenital cardiovascular abnormalities. [1]. The innate immune system includes acute phase proteins (APPs). The initial line of defense against microbes is the innate immune system that is maintained in all multicellular creatures. Additionally, this system becomes active after different types of tissue damage, which sets off immunological reactions and has a significant impact on the onset of cardiovascular disease. [2].

When inflammation occurs, plasma levels of APPs rise or fall. Numerous cytokines are released into the circulation by local inflammatory cells in response to injury. The majority of APPs have various physiological roles for the immune system, including preventing the growth of microorganisms, providing inverse effects on the inflammatory response, limiting infection by enclosing pathogens in local blood clots, increasing vascular permeability, and serving as

chemotactic factors for phagocytic cells. The APPs may serve as predictive biomarkers and play a role in inflammatory conditions, including cardiovascular diseases. [3].

Haptoglobin is one of the acute-phase proteins. It possesses antibacterial properties, functions as an antimicrobial or antioxidant, and influences numerous facets of the acute phase response. [4].

In individuals with VSD, reduced levels of haptoglobin may indicate a lack of antibacterial, antioxidant, or antimicrobial capabilities, along with a failure to limit iron loss by the kidney. Furthermore, lower blood haptoglobin levels demonstrate a high degree of accuracy in the biochemical identification of high-risk pulmonary embolisms. [5].

VSD is characterized by congested pulmonary capillaries caused by a left-to-right shunt. Reduced haptoglobin levels in VSD cases may represent the susceptibility of patients with VSD to infectious illnesses due to a variation in the acute phase response. [6].

The hemodynamic importance of a VSD is mostly influenced by its size, the pressure gradient between the left and right ventricular chambers, and vascular pulmonary resistance. The volume overload caused by VSD can develop into heart failure (HF). Heart failure has numerous repercussions, involving elevated death rates, long-term hospitalization, and a significant cost. Therefore, early identification and evaluation of VSD are vital for avoiding the occurrence of HF. [7]. The present work aimed to evaluate the value of haptoglobin in the detection of VSD, whether decompensated or not.

METHODS

Patients:

The patients' group comprised 36 children having VSD, of which 18 children had HF and 18 children were compensated. Heart failure was graded according to the Modified Ross classification as mild, moderate, and severe. [8]. A control group of 36 healthy children that were recruited with distributional matching to the patients regarding age and gender. Study participants were recruited at the Pediatric Cardiology Unit of Zagazig University Children's Hospital.

The study was conducted after obtaining approval from the Institutional Review Board (IRB), and written informed consent was taken from all cases' parents (IRB#6060/21-4-2020). The research was directed following the World Medical Association's Code of Ethics (Helsinki's Declaration) for human research.

Inclusion criteria included all patients with isolated VSD. Cases with complex congenital heart disease, hemolytic anemias, and co-existing inflammatory diseases of other organs or systems were excluded.

All patients of the studied groups were subjected to Full history taking, clinical evaluation, and laboratory tests [Complete blood count (CBC), C Reactive Protein (CRP), liver function (SGPT, SGOT, serum albumin], and serum electrolytes (Na, K, and Ca)).

Echocardiography

Echocardiography was done using an Epic Cvx Release 6 Philips machine. We utilized either S 8-3 or X 5-1 Megahertz probes. Measurements of LV systolic and diastolic dimensions, Aortic and LA dimensions, Fractional Shortening, and Ejection Fraction of LV were obtained with M-mode. Echocardiography from a short axis view of the parasternal window in agreement with the recommendations of the American Society of Echocardiography [9].

Haptoglobin level measurement:

Haptoglobin level was assessed by ELISA. Blood samples were taken from 72 participants with sterilized syringes in EDTA tubes, which were set aside to coagulate at room temperature for 10-20 minutes and then centrifuged for 20 minutes. The samples were saved at -20^{o} C. A Human haptoglobin kit with one original standard reagent was used. We diluted it according to instructions. We added the prepared samples, standards, and antibodies labeled with enzyme incubated for 60 minutes at 37 ^{o}c. Plates were washed five times, and chromogen solutions A and B were added and incubated for 10 minutes then, stop solution was added, and we measured the OD value

after 10 minutes then the standard curve linear regression equation was calculated.

STATISTICAL ANALYSIS

Data was analyzed employing SPSS version 26. Categorical variables were reported utilizing their absolute frequencies. Comparisons were made using the chi-square test, Fisher exact test, and Monte Carlo tests when needed. Kolmogorov-Smirnov test was developed to validate assumptions for parametric tests. Quantitative variables were defined employing means and SD or median and interquartile range, depending on the type of data. To compare quantitative data between the two groups, the independent sample t-test and Mann-Whitney test were applied. When $p<0.05$, the difference between the two groups was assessed using Turkey HSD. Pearson and Spearman rank correlation coefficients were applied based on the type of data. The ROC curve was employed to establish the optimal cutoff for a given quantitative parameter in the diagnosis of a specific health concern. $P<0.05$ was considered significant.

RESULTS

The VSD and control groups were homogenous regarding age and gender (Table 1). Respiratory rate and heart rate (HR), WBCs, platelets, albumin, SGOT, SGPT, and CRP were significantly higher among the VSD group. Body weight, body surface area, calcium, and haptoglobin were significantly lower among the VSD group (Table 2).

Although no significant differences were observed in LV systolic function, further analysis of diastolic function parameters, such as E/A ratio and E/E', may provide insights into early myocardial remodeling in VSD patients (Table 3). The elevated CRP levels in the VSD group may reflect an inflammatory response secondary to chronic pulmonary congestion. Future studies should evaluate whether CRP correlates with pulmonary artery pressures in these patients, the mean haptoglobin level in the VSD without HF group was significantly lower (7.21 ± 2.14 mg/dl) than in the control group (9.92 ± 1.31 mg/dl), with a p-value of 0.006, indicating statistical significance. (Table 4). Platelets, SGOT, and CRP were elevated, while there was a substantial decline of haptoglobin in the decompensated VSD group (Table 5).

A significant inverse correlation was observed between plasma haptoglobin levels and heart failure severity ($r = -0.644$, $p < 0.001$), respiratory rate, heart rate, WBCs, platelets, albumin, SGPT, SGOT, and CRP. There was a significant positive relationship between haptoglobin and body weight (Table 6).

The optimal haptoglobin cutoff for diagnosing VSD was ≤8.045 mg/dL, with an area under the curve (AUC) of 0.864, sensitivity of 80.6%, and specificity of 94.4%. (Table 7, Supplementary Figure 1)

Table (1) : Statistical comparison of the demographics of research groups:

	VSD group	**Control group**	χ^2	**p**
	N=36 (%)	**N=36 (%)**		
Sex:				
Female	16 (44.4%)	18 (50%)	0.233	0.637
Male	20 (55.6%)	18 (50%)		
	Median (IQR)	**Median (IQR)**	Z	p
Age (month)	12(2.25 – 34.5)	24(8.5 – 48)	-1.899	0.06

IQR : interquartile range, χ^2 : Chi square test, Z : Mann Whitney test

Table (2): Comparison between the studied groups regarding clinical and laboratory data

	VSD group **N=36 (%)**	Control group **N=36 (%)**	Z/t	p
Respiratory rate (bpm)	43.0 ± 9.18	28.19 ± 5.75	8.202	<0.001**
Heart rate (Bpm)	123.06 ± 25.42	85.22 ± 17.7	7.329	<0.001**
Height (cm)	74.22 ± 17.61	79.31 ± 20.84	-1.118	0.267
Hemoglobin (g/dl)	10.51 ± 1.21	10.77 ± 2.03	-0.663	0.509
WBCS ($10^3/mm^3$)	7.37 ± 2.23	5.67 ± 1.36	3.885	<0.001**
Albumin (g/dl)	3.43 ± 0.4	3.16 ± 0.19	3.703	<0.001**
SGPT (U/L)	42.89 ± 1.43	33.39 ± 6.89	8.098	0.653
Sodium (mEq/L)	135.69 ± 3.87	135.75 ± 3.26	-0.066	0.948
Potassium (mg/dl)	3.74 ± 0.75	3.96 ± 0.86	-1.139	0.259
Calcium (mg/dl)	8.19 ± 1.38	8.84 ± 1.01	-2.279	0.026*
Haptoglobin (mg/dl)	7.21 ± 2.14	9.92 ± 1.31	-6.473	<0.001**
Weight (kg)	8.75(4 – 11)	12(8.25 – 15)	-2.625	0.009*
BodySurfaceArea (m^2)	0.4(0.26 – 0.53)	0.47(0.39 – 0.65)	-2.096	0.036*
Platelet ($10^3/mm^3$)	250(150 – 300)	160(150 – 173.75)	-2.738	0.005*
SGOT (U/L)	85(45 – 100)	42.5(40 – 45)	-6.131	<0.001**
CRP (mg/dL)	0.5(0 – 2)	0(0 – 0)	-5.056	<0.001**

CRP: C Reactive Protein,*p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, t : independent sample t test, Z :Mann Whitney test

Table (3) : Comparison between the studied groups regarding cardiac dimensions and LV systolic functions

	VSD group	Control group	Z	p
	Median (IQR)	**Median (IQR)**		
PA (mm)	14(12 – 16.75)	14(11.63 – 15)	-0.815	0.415
LPA (mm)	7(5 – 10.75)	7(6.63 – 8.38)	-0.222	0.824
RPA (mm)	7(6 – 9.5)	8(7 – 9)	-1.534	0.125
LA (mm)	21(16 – 27.75)	20(15.5 – 22)	-1.424	0.155
AO (mm)	14(12 – 19.75)	16(15 – 17.75)	-0.831	0.406
LVED (mm)	26(22 – 36.75)	30(24.25 – 32.75)	-0.813	0.416
LVES (mm)	16(15 – 22.75)	18(14.25 – 21.75)	-0.543	0.587
	Mean ± SD	**Mean ± SD**	T	P
EF (%)	71.56 ± 8.19	72.61 ± 7.02	-0.587	0.559
FS (%)	40.78 ± 5.9	41.19 ± 7.18	-0.269	0.789

AO: Aortic Root dimension, EF : Ejection Fraction, FS : Fractional Shortening percentage, IQR: interquartile range, LA: Left Atrium dimension, LPA: Left Pulmonary Artery dimension, LVED : Left Ventricular End Diastole diameter, LVES: Left Ventricular End Systole diameter, PA : Pulmonary Artery dimension, RPA: Right Pulmonary Artery dimension, t :independent sample t test, Z :Mann Whitney test

Table (4) : Comparison between VSD without HF group and control group regarding some laboratory and echocardiographic data

	VSD without HF group	Control group	t	P
	Mean ± SD	**Mean ± SD**		
SGPT (U/L)	43.0 ± 1.03	33.39 ± 6.89	81.87	<0.001**
EF (%)	69.06 ± 8.2	72.61 ± 7.02	-1.658	0.103
FS (%)	38.39 ± 5.54	41.19 ± 7.18	-1.453	0.152
	Median (IQR)	**Median (IQR)**	**Z**	**P**
CRP (mg/dL)	0.5(0 – 2)	0(0 – 0)	-3.414	<0.001**
Platelet ($10^3/mm^3$)	150(147.5 – 193.75)	160(150 – 173.75)	-1.092	0.275
SGOT (U/L)	45(45 – 81.25)	42.5(40 – 45)	-4.099	<0.001**
Haptoglobin (mg/dl)	7.21 ± 2.14	9.92 ± 1.31	-2.993	0.006*

CRP: C Reactive Protein, EF: Ejection fraction, FS: Fractional shortening, IQR: interquartile range, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, t: independent sample t test, Z: Mann Whitney test

Table (5**):** Comparison between VSD with Heart Failure group and Control group regarding laboratory data

	VSD with HF group	Control group	t	p
	Mean ± SD	**Mean ± SD**		
SGPT (U/L)	42.78 ± 1.77	33.39 ± 6.89	8.098	0.653
EF (%)	74.06 ± 7.59	72.61 ± 7.02	0.694	0.491
FS (%)	43.17 ± 5.37	41.19 ± 7.18	1.029	0.308
	Median (IQR)	**Median (IQR)**	**Z**	**p**
CRP (mg/dL)	1(0.5 – 2)	0(0 – 0)	-5.7	<0.001**
SGOT (U/L)	90 (85 – 100)	42.5(40 – 45)	-6.004	<0.001**
Platelet (10^3/mm^3)	295 (295– 300)	160(150 – 173.75)	-5.731	<0.001**
Haptoglobin (mg/dl)	6.133 ± 1.58	9.92 ± 1.31	-9.339	<0.001**

CRP: C Reactive Protein, EF: Ejection fraction, FS: Fractional shortening, HF: Heart failure, IQR: interquartile range, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, t: independent sample t test, VSD : Ventricular septal defect, Z :Mann Whitney test

Table (6**) Correlation between haptoglobin and the studied parameters:**

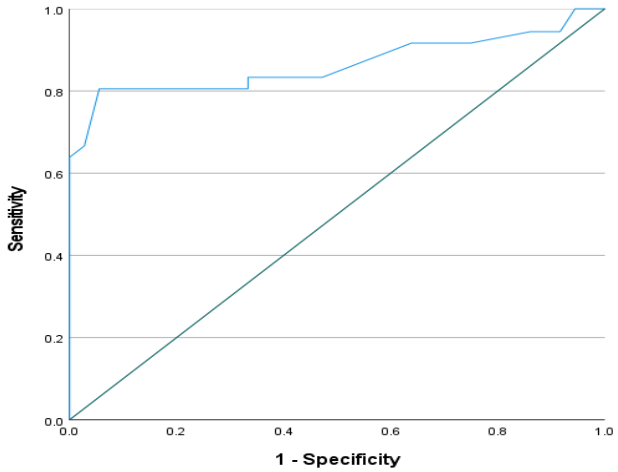
	R	P
Age (month)	0.18¥	0.131
HF grades	**-0.644**¥	**<0.001****
Respiratory rate	**-0.543**	**<0.001****
Heart rate	**-0.489**	**<0.001****
Gestational age (week)	0.034	0.776
Height (cm)	0.005	0.966
Weight (kg)	**0.247**¥	**0.036***
BodySurface Area (m^2)	0.184¥	0.121
WBCS (10^3/mm^3)	**-0.419**	**<0.001****
Platelets (10^3/mm^3)	**-0.59**	**<0.001****
Albumin (g/dl)	**-0.426**	**<0.001****
SGPT (U/L)	**-0.387**	**<0.001****
SGOT (U/L)	**-0.705**	**<0.001****
Sodium (mEq/L)	-0.077	0.52
Potassium (mg/dl)	-0.024	0.843
Calcium (mg/dl)	-0.088	0.461
CRP (mg/dL)	**-0.578**¥	**<0.001****

CRP:C Reactive protein, *p<0.05 is statistically significant, **p≤0.001 is statistically highly significant, r: Pearson correlation coefficient, ¥Spearman rank correlation coefficient, SGOT : serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamic pyruvic transaminase, WBCs: white blood cells

Table (7) Performance of Haptoglobin in diagnosis of VSD:

Cutoff	AUC	95% CI	Sensitivity	Specificity	p
≤8.045 mg/dl	0.864	0.77 – 0.959	80.6%	94.4%	<0.001**

AUC : area under curve, CI :Confidence interval , *p≤0.001 is statistically highly significant



Supplementary Figure (1) Haptoglobin's diagnostic performance in the context of VSD, as seen by the ROC curve

DISCUSSION

The majority of APPs have various physiological roles for the immune system, including preventing the growth of microorganisms, providing negative feedback on the inflammatory response, limiting infection by enclosing pathogens in local blood clots, increasing vascular permeability, and serving as chemotactic agents for phagocytic cells. APPs may be utilized as disease prediction markers. [10].

Hepatocytes' synthesis of acute phase proteins is controlled by several soluble factors, including interleukin-1 (IL-1), tumor necrosis factor (TNF), and hepatocyte stimulating factor (HSF). Only HSF could generate all acute phase proteins. It was shown that IL-6 can act as HSF. It can produce acute-phase proteins such as fibrinogen, α1-acid glycoprotein, α1-antichymotrypsin, and haptoglobin. [11].

In individuals with VSD, decreased levels of haptoglobin may indicate a lack of antibacterial, antioxidant, or antimicrobial capabilities, along with a failure to limit the renal iron loss and, subsequently, more likelihood of renal hemoglobin damage. Furthermore, lower blood haptoglobin levels demonstrate a high degree of accuracy in the biochemical identification of high-risk pulmonary embolisms. [12].

VSD is characterized by congested pulmonary capillaries caused by a left-to-right shunt. According to Mavroudis et al. [6] Reduced haptoglobin levels in VSD cases may contribute to lung injury induced by this left-to-right shunt. Haptoglobin level modification may also increase the susceptibility of patients with VSD to infections due to a variation in the acute phase response. [6].

Haptoglobin was reduced in our patients with VSD compared with the control group (7.21 $\pm$ 2.14 vs 9.92 $\pm$ 1.31 (P <0.001, table 2). The reduction in haptoglobin levels in VSD patients may be due to increased hemolysis from turbulent blood flow across the septal defect, leading to greater haptoglobin consumption. Additionally, systemic inflammation and oxidative stress in heart failure may contribute to altered acute-phase protein dynamics. In line with our findings, Xuan et al. [14], reported downregulation of haptoglobin in patients with VSD. Zhang et al. [13], also found that haptoglobin was reduced in patients with VSD.

Insenser et al. [5] indicated that individuals with VSD had decreased levels of haptoglobin. They also demonstrated that decreased serum haptoglobin values had satisfactory precision in the diagnosis of pulmonary embolism.

Our results revealed that haptoglobin was reduced in our patients with decompensated VSD compared with the control group (table 5). There was a significant inverse association between plasma haptoglobin and heart failure

grades, respiratory rate, heart rate, WBCs, platelets, albumin, SGPT, SGOT, and CRP. On the contrary, a significant positive association was present between haptoglobin level and body weight (Table 6).

While our study found a decrease in haptoglobin levels in children with decompensated VSD, Karim et al. [15] reported increased haptoglobin in adult CHF patients. This discrepancy may be attributed to differences in age, underlying cardiac pathology, and haptoglobin polymorphisms, which influence its response to inflammation.

Because haptoglobin and inflammation are closely related, Rajendiran et al. [16] examined the plasma expressions of inflammatory markers in individuals with CHF. They found that Elevated expressions of inflammation and oxidative stress markers are linked to HF. When comparing CHF cases to healthy controls, the haptoglobin 2-2 phenotype was similarly linked to higher plasma expressions of oxidative stress markers. [16]. A positive association was found between haptoglobin concentrations and circulating indicators of systemic inflammation and oxidative stress. [17].

A clinical investigation conducted by Holme et al. [18] Revealed that in a healthy group, increased haptoglobin was a predictor of the risk of cardiac disease.

Brunetti et al. [19] examined how several APPs affected LV systolic function, and they discovered that higher APP levels, including haptoglobin, had a negative association with LVEF. They concluded that a greater prevalence of acute HF and LV systolic dysfunction might be connected to elevated haptoglobin concentrations.

Sveinsdottir et al. [20] reported that higher levels of some inflammatory proteins, including haptoglobin, were linked to myocardial infarction, HF, stroke, and other cardiovascular consequences.

Inversely, Haas et al. [21] demonstrated that the onset of HF was predicted by low Hp values recorded at the time of presentation. According to their conclusions, lower haptoglobin concentrations may cause more damage to heart tissue and, as a consequence, might be linked to worse outcomes. In line with this, Arslan et al. [22] demonstrated how a lack of haptoglobin affected heart function and tissue repair.

In this study, the best cutoff of haptoglobin in diagnosis VSD was ≤8.045 mg/dl, the area under the curve was 0.864, with 80.6% sensitivity and 94.4% specificity (table 7, figure 1). Our findings indicate that haptoglobin might be a reliable marker for VSD diagnosis.

Lu et al. [23] discovered that poorer outcomes and a higher chance of mortality were linked to lower haptoglobin concentrations. Compared to individuals with haptoglobin levels of 177.1 ng/mL or above, there was a greater number of non-survivors in the group with levels below 177.1ng/ml.

CONCLUSION

Haptoglobin levels were reduced in VSD cases. An inverse association was found between haptoglobin and severity of heart failure. Plasma haptoglobin level was 80.6 % sensitive and 94.4% specific in the diagnosis of VSD. Larger multicenter studies are required to validate our findings.

Conflict of Interest or financial disclosure: No potential conflict of interest to be reported by the authors.

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Citation

Abd El-Aziz, L., AbouZeid, H., Khalifa, N., Farrag, L. Plasma Haptoglobin Level as a Diagnostic Biomarker in Children with Ventricular Septal Defect. ***Zagazig University Medical Journal*****, 2025; (2225-2232): -. doi: 10.21608/zumj.2025.359414.3837**