

# World Journal of *Cardiology*

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## EDITORIAL

- 673 Balancing bleeding, thrombosis and myocardial injury: A call for balance and precision medicine for aspirin in neurosurgery  
*Niyogi SG, Batta A, Mohan B*
- 677 Catheter ablation using pulsed-field energy: Do we finally have the magic wand to defeat atrial fibrillation?  
*Cristiano E, Ali H, Celentano E, Cappato R*
- 683 Thoughts on recent articles on cardiopulmonary resuscitation  
*Sunder T*

## REVIEW

- 689 Molecular and metabolic landscape of adenosine triphosphate-induced cell death in cardiovascular disease  
*Wang W, Wang XM, Zhang HL, Zhao R, Wang Y, Zhang HL, Song ZJ*

## MINIREVIEWS

- 707 E-cigarettes and arterial health: A review of the link between vaping and atherosclerosis progression  
*Hassan M, Vinagolu-Baur J, Li V, Frasier K, Herrick G, Scotto T, Rankin E*

## ORIGINAL ARTICLE

## Retrospective Study

- 720 Independent prognostic value of lipocalin-2 in congenital heart disease-associated pulmonary artery hypertension  
*Guo ZK, Chen PG, Li YX, Jiao H, Kong XH, Bai S, Li XF, Liu AJ, Wang GL*
- 731 Trends in cardiovascular and cerebrovascular health scores in the Kailuan population from 2006 to 2011  
*Yu Y, Zhang ZX, Yin SF, Wu SL, Liu ZJ*
- 740 Role of a new inflammation predictor in predicting recurrence of atrial fibrillation after radiofrequency catheter ablation  
*Wang YJ, Liu KS, Meng XJ, Han XF, Nie LJ, Feng WJ, Chen YB*

## Observational Study

- 751 Nocturnal sentry duty and cardiometabolic characteristics in armed forces personnel  
*Lin YP, Hsu YC, Lin KH, Tsai KZ, Chu CC, Lin YC, Lin GM*

**CASE REPORT**

- 760** Right ventricular diverticulum following a pulmonary valve placement for correction of tetralogy of Fallot: A case report  
*Martinez Juarez D, Gomez Monterrosas O, Tlecuil Mendoza A, Zamora Rosales F, Álvarez Calderón R, Cepeda Ortiz DA, Espinosa Solis EE*
- 768** Nicorandil as a promising therapeutic option for ventricular arrhythmia: A case report and review of literature  
*Bai LY, Zhao M, Ma KY*

**LETTER TO THE EDITOR**

- 776** Comparative breakthrough: Umbilical cord mesenchymal stem cells *vs* bone marrow mesenchymal stem cells in heart failure treatment  
*Li P*
- 781** Sodium-dependent glucose transporter 2 inhibitors: Transforming diabetic cardiomyopathy management  
*Cheng CH, Hao WR, Cheng TH*

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## Retrospective Study

## Independent prognostic value of lipocalin-2 in congenital heart disease-associated pulmonary artery hypertension

Zhang-Ke Guo, Ping-Gui Chen, Yao-Xuan Li, Hong Jiao, Xiao-Hui Kong, Song Bai, Xiao-Feng Li, Ai-Jun Liu, Guo-Liang Wang

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**Abstract****BACKGROUND**

Timely and accurate evaluation of the patient's pulmonary arterial pressure (PAP) is of great significance for the treatment of congenital heart disease. Currently, there is no non-invasive gold standard method for evaluating PAP.

**AIM**

To assess the prognostic value of lipocalin-2 (LCN2) in relation to PAP in patients with congenital heart disease associated with pulmonary artery hypertension.

**METHODS**

We conducted a retrospective analysis of 69 pediatric patients diagnosed with

ventricular septal defects. The patients' clinical and laboratory data were collected. The serum LCN2 concentrations were compared between the pulmonary arterial hypertension (PAH) group and the nonPAH group. The correlation of LCN2 concentration with PAH classification was evaluated using binary logistic regression analysis. The receiver operating characteristic (ROC) curve was used to evaluate the diagnostic potential of LCN2 for PAH.

## RESULTS

Serum LCN2 concentration significantly correlated with patients' mean PAP ( $r = 0.544$ ,  $P < 0.001$ ), but not correlated with creatinine ( $P = 0.446$ ) or blood urea nitrogen ( $P = 0.747$ ). LCN2 levels were significantly correlated with PAH in both univariate [odds ratio (OR) 1.107, 95% CI: 1.033-1.185,  $P = 0.004$ ] and multivariate regression analysis (OR 1.150, 95% CI: 1.027-1.288,  $P = 0.015$ ). ROC curve analysis revealed an area under the curve of 0.783 for LCN2. At the cutoff value of 19.42 ng/mL, the sensitivity and specificity of LCN2 for diagnosing PAH is 90.19% and 55.56%, respectively. LCN2 concentration also significantly correlated with the post-repair mean PAP in patients with congenital heart disease ( $r = 0.532$ ,  $P = 0.009$ ).

## CONCLUSION

LCN2 is emerging as a candidate biomarker for assessing PAP in patients with congenital heart disease. Its high sensitivity in diagnosing PAH makes it a valuable tool in patient management.

**Key Words:** Congenital heart disease; Pulmonary arterial hypertension; Lipocalin-2; Endothelin-1; Biomarker

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**Core Tip:** This retrospective study demonstrates that lipocalin-2 (LCN2) blood levels significantly correlated with the mean pulmonary arterial pressure of patients with congenital heart disease (CHD). In particular, LCN2 was significantly correlated with the post-repair mean pulmonary arterial pressure of CHD patients. LCN2 has emerged as a candidate biomarker for CHD, and its high sensitivity to pulmonary arterial hypertension diagnosis makes it highly valuable in patient management.

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## INTRODUCTION

Pulmonary arterial hypertension (PAH) is characterized by a sustained increase in pulmonary arterial pressure (PAP) and pulmonary vascular resistance[1]. Among the different forms of pediatric PAH, PAH caused by congenital heart disease (PAH-CHD) is particularly significant.

Timely intervention to block abnormal left-to-right shunting in the heart can usually normalize elevated PAP. However, partial patients continue to experience persistent or even worsening PAH, which may be attributed to delayed shunt correction[2,3]. Timely and accurate evaluation of PAP is crucial for the management of congenital heart disease (CHD) patients with left-to-right shunt. At present, evaluations of PAP through echocardiography faces notable limitations. For instance, measurements obtained *via* echocardiography often significantly differ from those obtained through right heart catheterization. Additionally, echocardiography has proven inadequate in predicting mortality in PAH patients, particularly those classified as New York Heart Association functional class III-IV with RV dilation[4,5]. There remains a need for reliable non-invasive gold standard methods to assess PAP.

Lipocalin-2 (LCN2), also known as neutrophil gelatinase-associated lipocalin, is a 25-kDa protein that belongs to the lipocalin family. LCN2 is expressed in various tissues, including the liver, kidney, lung, and adipose tissue, playing pivotal roles in diverse physiological and pathological processes[6,7]. We previously demonstrated that LCN2 is up-regulated in PAH-CHD, where it promotes pulmonary artery smooth muscle cell proliferation and helps resist apoptosis [8-10]. LCN2 has also been reported play roles in Kawasaki disease-related PAH[11]. These studies suggest that LCN2 may play an important role in PAH and serve as a potential biomarker for PAH. Furthermore, LCN2 has been identified as a biomarker for acute kidney injury[12,13] and is involved in the development of chronic kidney diseases, including diabetic nephropathy and renal fibrosis[14]. Given the strong physiological and pathological connections between the heart and kidneys[15,16], it is necessary to clarify whether LCN2 upregulation in PAH-CHD patients is a consequence of renal dysfunction.

The aim of the present study was to evaluate the independent predictive value of LCN2 on PAP in a series of consecutive pediatric patients with ventricular septal defect (VSD), for whom right ventricular catheterization pressure, blood cell counts, and biochemical parameters were accessible. Additionally, we compared the predictive values of LCN2 and endothelin-1 (ET-1), a candidate biomarker for PAH[17].



## MATERIALS AND METHODS

### Subjects

The present study retrospectively collected data from Chinese children with CHD who received treatment at Beijing Children's Hospital over a 4-year period from January 2019 to December 2022. The clinical and laboratory data of the patients were extracted from hospital registry systems by two academic surgeons. This study was approved by the Beijing Children's Hospital Ethics Committee, and all patients or their parents or legal guardians provided written informed consent.

We collected data from pediatric patients who were primarily diagnosed with VSD following cardiac surgery. The inclusion criteria comprised: (1) Surgical repair of VSD; (2) Age less than 72 months; (3) Measurement of PAP *via* intra-operative right ventricular catheterization; and (4) Preoperative serum samples preserved in the biologic sample bank of our hospital. The exclusion criteria included: (1) Cases with abnormal cardiac structures other than VSD or VSD accompanied with atrial septal defect ( $n = 51$ ); (2) Cases with heart diseases other than CHD ( $n = 1$ ); (3) Cases with other systemic diseases ( $n = 2$ ); and (4) Cases that received medications influencing cardiac or renal function during the last 3 months prior to surgery ( $n = 0$ ). Overall, 69 patients (41 females and 28 males) were included in this study.

### ELISA assays

The serum levels of LCN2 and ET-1 were measured using LCN2/NGAL Human ELISA Kit (EHLN2; Thermo Fisher, Waltham, MA, United States) and ET-1 Human ELISA Kit (EIAET1; Thermo Fisher) following the manufacturer's instructions.

### Statistical analysis

The mean PAP (mPAP) was measured through intra-operative right ventricular catheterization. PAH is defined as mPAP  $> 20$  mmHg according to the classification established at the 6<sup>th</sup> World Symposium of Pulmonary Hypertension[18]. Patients were divided into the PAH group and nonPAH group based on their mPAP values. The diameter of the defect was measured during surgery, and for patients with multiple defects, the defect diameter was calculated based on the total area of all defects.

Continuous variables are expressed as median (Q1, Q3), while categorical variables are expressed as proportion. The Mann-Whitney *U* test was utilized for comparisons between two independent groups for numerical variables, and the chi-square test was employed for categorical variables, such as the sex of the patients. The Fisher exact test was applied when at least one expected count was less than 5. Pearson correlation was determined between two continuous variables, and Spearman correlation was used when categorical data were included. Odds ratio (OR) and 95%CI were calculated using binary logistic regression analysis. Variables with a *P* value less than 0.15 in univariate regression were included in the multivariate regression model. The receiver operating characteristic (ROC) curve was employed to evaluate the diagnostic values of the variables. A bilateral *P* value of  $< 0.05$  was considered statistically significant. Statistical analyses were performed using SPSS 25.0 (IBM Corp., Armonk, NY, United States), Medcalc 19.0 or GraphPad Prism 8.0.

## RESULTS

### Patients' characteristics

The clinical and laboratory characteristics of the PAH and nonPAH patients are summarized in Table 1. A total of 69 children with CHD participated in this study, including 41 (59.4%) females and 28 (40.6%) males, with a median age of 14.6 months (range 3 months to 55 months). Significant differences were observed between the nonPAH and PAH group in creatinine, blood urea nitrogen (BUN), glucose, mPAP, LCN2 and ET-1. There were no significant differences in sex, age, systolic blood pressure, diastolic blood pressure, ejection fraction, defect diameter, or other laboratory factors between the two groups.

### Significant difference in renal function between nonPAH and PAH groups

As shown in Table 1, there were significant differences in median values of creatinine (21.8  $\mu\text{mol/L}$  vs 27.8  $\mu\text{mol/L}$ ,  $P < 0.001$ ) and BUN (3.0 mmol/L vs 4.2 mmol/L,  $P = 0.015$ ) between the nonPAH and PAH groups. Pearson correlation analysis demonstrated a significant correlation between mPAP and both creatinine ( $r = 0.389$ ,  $P < 0.001$ ) and BUN ( $r = 0.328$ ,  $P = 0.006$ ), as shown in Table 2. These results suggest that the PAH group exhibits poorer renal function compared to the nonPAH group among CHD children.

### Serum LCN2 concentration significantly correlated with mPAP of VSD patients

According to Table 2, there was a significant correlation between LCN2 and mPAP ( $r = 0.544$ ,  $P < 0.001$ ) in VSD children. However, LCN2 does not significantly correlate with creatinine ( $r = 0.094$ ,  $P = 0.446$ ) or BUN ( $r = -0.040$ ,  $P = 0.747$ ). Even after excluding confounding factors in multivariate regression analysis, LCN2 remained uncorrelated with creatinine or BUN, as shown in Table 3.

To further explore the relationship between LCN2 and PAH, binary logistic regression analysis was conducted. In the univariate regression analysis (Table 4), variables with a *P* value less than 0.15 (include age, creatinine, white blood cell and LCN2) were included in the multivariate logistic regression model. BUN was excluded in the model due to its significant collinearity with creatinine. The diameter of the defect was also included in the multivariate model based on

**Table 1** Baseline characteristics of the nonpulmonary arterial hypertension and pulmonary arterial hypertension patients

Variables	Total number	nonPAH	PAH	P value
Number	69	18	51	-
Sex, number of males	69	7 (38.9)	21 (41.2)	0.866
Age in months	69	8.5 (5.4, 12.0)	11.0 (7.0, 19.0)	0.094
BMI	68	15.4 (13.8, 17.4)	15.1 (14.1, 16.6)	0.451
Creatinine in $\mu\text{mol/L}$	68	21.8 (18.0, 26.5)	27.8 (24.3, 33.6)	< 0.001
BUN in $\text{mmol/L}$	68	3.0 (2.1, 3.7)	4.2 (2.8, 5.1)	0.015
Albumin in $\text{g/L}$	67	42.6 (39.6, 43.7)	43.5 (41.4, 45.3)	0.243
Glucose in $\text{mmol/L}$	65	4.6 (4.1, 5.0)	4.1 (3.8, 4.4)	0.036
Hemoglobin in $\text{g/L}$	69	116 (101, 123)	118 (108, 128)	0.448
Platelets as $10^9/\text{L}$	69	276 (247, 314)	267 (221, 344)	0.995
White blood cells as $10^9/\text{L}$	46	8.3 (5.7, 9.7)	8.7 (7.5, 11.0)	0.140
SBP in $\text{mmHg}$	66	93.0 (84.5, 95.0)	95.0 (86.5, 101.5)	0.144
DBP in $\text{mmHg}$	66	55.0 (48.5, 60.0)	55.0 (45.0, 60.0)	0.860
EF as %	67	65.0 (62.0, 66.3)	65.0 (65.0, 69.5)	0.072
Diameter in $\text{mm}$	66	10.0 (7.5, 13.0)	10.0 (8.0, 14.8)	0.219
mPAP in $\text{mmHg}$	69	17.7 (16.7, 18.8)	29.4 (24.6, 40.1)	< 0.001
LCN2 in $\text{ng/mL}$	69	19.3 (16.9, 27.6)	33.4 (23.9, 46.3)	< 0.001
ET1 in $\mu\text{g/mL}$	69	0.14 (0.07, 0.31)	0.30 (0.10, 0.72)	0.049

Data are  $n$  (%). Sex is expressed as a proportion; continuous variables are expressed as median (Q1, Q3). Diameter means the diameter of the defect, which was measured during surgery. BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; PAH: Pulmonary arterial hypertension; SBP: Systolic blood pressure.

its clinical relevance. As shown in **Figure 1**, after adjusting for confounding variables, LCN2 was significantly correlated with PAH (OR 1.150, 95%CI: 1.027-1.288,  $P = 0.015$ ). LCN2 remained significantly correlated with PAH (OR 1.123, 95%CI: 1.032-1.222,  $P = 0.007$ ) after excluding the white blood cell count from the model, given the considerable missing values for this parameter and its insignificance in relation to PAH.

### LCN2 exhibits a higher diagnostic potential for PAH in patients with VSD than ET-1

From **Table 2**, it is evident that both LCN2 and ET-1 are significantly correlated with mPAP in VSD children. However, in the binary logistic regression analysis, ET-1 did not show a significant correlation with mPAP in either the univariate (**Table 4**) or multivariate (**Table 5**) analyses. These results indicate that LCN2 exhibits a strong correlation with mPAP compared to ET-1. The diagnostic values of LCN2 and ET-1 for predicting PAH were evaluated using the ROC curve method. As illustrated in **Figure 2A**, LCN2 demonstrated a larger area under the curve (AUC) of 0.783 compared to 0.657 for ET-1 when predicting PAH in CHD patients. For LCN2, with a best cutoff value of 19.42  $\text{ng/mL}$ , the sensitivity, specificity and Yonden's index for diagnosing PAH were 90.19%, 55.56% and 0.4575, respectively. Conversely, for ET-1, with a best cutoff value of 0.39  $\mu\text{g/mL}$ , the sensitivity, specificity and Yonden's index in diagnosing PAH were 45.10%, 94.44% and 0.3954, respectively (**Table 6**).

### LCN2 concentration significantly correlated with the post-repair mPAP of VSD patients

The post-repair mPAP values (intra-operative) of 23 patients were recorded. All 23 patients exhibited a decrease in post-repair mPAP compared to pre-repair levels. Among these, seven patients were classified as nonPAH and 16 as PAH based on their post-repair mPAP values. Notably, four patients transitioned from pre-repair PAH to post-repair nonPAH. **Table 7** shows that correlation analysis indicates a significant relationship between pre-repair mPAP and both post-repair mPAP ( $r = 0.471$ ,  $P = 0.023$ ) and mPAP decrease ( $r = 0.883$ ,  $P < 0.001$ ) following repair surgery. LCN2 was significantly correlated with post-repair mPAP ( $r = 0.532$ ,  $P = 0.009$ ), but it did not show a significant correlation with mPAP decrease ( $r = 0.181$ ,  $P = 0.407$ ). Conversely, ET-1 was not correlated with either post-repair mPAP ( $r = 0.140$ ,  $P = 0.523$ ) or mPAP decrease ( $r = 0.298$ ,  $P = 0.167$ ). From **Figure 2B**, we can see that the LCN2 concentration in post-repair PAH patients was higher than that in nonPAH patients (31.6  $\text{ng/mL}$  vs 25.5  $\text{ng/mL}$ , median value), although this difference was not statistically significant ( $P = 0.154$ ).



**Table 2 Correlations of mean pulmonary artery pressure, lipocalin-2 and endothelin-1 with clinical variables**

Variables	mPAP		LCN2		ET-1	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Sex	0.087	0.475	0.031	0.800	-0.115	0.347
Age in months	0.298	0.013	0.319	0.008	0.048	0.698
BMI	-0.089	0.483	-0.128	0.310	-0.248	0.046
Creatinine in $\mu\text{mol/L}$	0.389	0.001	0.094	0.446	-0.156	0.205
BUN in $\text{mmol/L}$	0.328	0.006	-0.040	0.747	-0.070	0.568
Albumin in $\text{g/L}$	0.066	0.594	-0.072	0.563	-0.238	0.052
Glucose in $\text{mmol/L}$	-0.174	0.166	0.021	0.869	-0.004	0.973
Hemoglobin in $\text{g/L}$	0.217	0.074	0.080	0.514	-0.173	0.156
Platelets as $10^9/\text{L}$	0.007	0.958	-0.128	0.293	-0.098	0.422
White blood cells as $10^9/\text{L}$	0.345	0.019	0.291	0.050	0.107	0.480
SBP in $\text{mmHg}$	0.135	0.280	0.074	0.554	0.033	0.795
DBP in $\text{mmHg}$	0.097	0.438	0.106	0.399	0.003	0.983
EF as %	-0.107	0.388	-0.176	0.155	-0.021	0.864
Diameter in $\text{mm}$	0.371	0.002	0.081	0.516	0.230	0.063
mPAP in $\text{mmHg}$	-	-	0.544	< 0.001	0.508	< 0.001
LCN2 in $\text{ng/mL}$	0.544	< 0.001	-	-	0.427	< 0.001
ET1 in $\mu\text{g/mL}$	0.508	< 0.001	0.427	< 0.001	-	-

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; SBP: Systolic blood pressure.

**Table 3 Multivariate logistic regression analysis to define the correlation between lipocalin-2 and renal function in ventricular septal defect patients**

Variables	Creatinine <sup>1</sup>			BUN <sup>1</sup>		
	OR	95%CI	<i>P</i> value	OR	95%CI	<i>P</i> value
Age in months	1.077	1.006-1.153	0.034	1.117	1.010-1.235	0.031
BMI	1.226	0.913-1.648	0.175	-	-	-
Albumin in $\text{g/L}$	1.089	0.901-1.315	0.378	1.016	0.837-1.232	0.875
Glucose in $\text{mmol/L}$	-	-	-	0.635	0.294-1.371	0.248
Hemoglobin in $\text{g/L}$	-	-	-	1.042	0.992-1.094	0.102
mPAP in $\text{mmHg}$	1.065	0.992-1.142	0.082	1.086	1.008-1.170	0.030
LCN2 in $\text{ng/mL}$	0.962	0.914-1.014	0.147	0.972	0.922-1.025	0.294

<sup>1</sup>Variable was binarized based on its median value.

BMI: Body mass index; BUN: Blood urea nitrogen; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; OR: Odds ratio.

## DISCUSSION

PAH associated with CHD is a subgroup of pulmonary hypertension (PH). While there are established expert guidelines for managing PH, there is a notable lack of evidence specifically addressing the management of PAH in patients with CHD. The advancements in the management of CHD have significantly improved survival rates, allowing many children to reach adulthood. However, a considerable number of these children experience various cardiac sequelae, including persistent or progressive PAH[19]. Therefore, timely and accurate assessment of PAP levels is crucial for the effective management of patients with CHD. Unfortunately, there are currently no robust biomarkers available for evaluating PAP, particularly in the context of CHD patients. This underscores the importance of identifying and assessing new

**Table 4 Univariate logistic regression analysis to determine the related factors of pulmonary arterial hypertension and lipocalin-2**

Variables	Correlation with PAH			Correlation with LCN2 <sup>1</sup>		
	OR	95%CI	P value	OR	95%CI	P value
Sex, males	1.1	0.366-3.303	0.865	1.212	0.463 ± 3.172	0.696
Age in months	1.05	0.985-1.119	0.137	1.050	1.002 ± 1.101	0.043
BMI	0.868	0.669-1.127	0.289	0.859	0.676 ± 1.091	0.213
Creatinine in $\mu\text{mol/L}$	1.204	1.066-1.359	0.003	1.021	0.952 ± 1.094	0.566
BUN in $\text{mmol/L}$	1.684	1.089-2.606	0.019	0.967	0.711 ± 1.316	0.832
Albumin in $\text{g/L}$	1.114	0.942-1.317	0.205	1.050	0.930 ± 1.186	0.432
Glucose in $\text{mmol/L}$	0.648	0.346-1.213	0.175	0.763	0.431 ± 1.350	0.353
Hemoglobin in $\text{g/L}$	1.017	0.982-1.053	0.345	1.006	0.977 ± 1.036	0.686
Platelets as $10^9/\text{L}$	1	0.995-1.006	0.887	0.999	0.995 ± 1.004	0.841
White blood cells as $10^9/\text{L}$	1.259	0.960-1.651	0.096	1.111	0.908 ± 1.361	0.306
SBP in $\text{mmHg}$	1.036	0.984-1.091	0.176	1.018	0.977 ± 1.060	0.401
DBP in $\text{mmHg}$	0.998	0.955-1.044	0.944	1.027	0.983 ± 1.073	0.239
EF as %	1.099	0.966-1.250	0.152	0.932	0.834 ± 1.040	0.207
Diameter in $\text{mm}$	1.106	0.944-1.296	0.211	1.011	0.883 ± 1.157	0.877
mPAP in $\text{mmHg}$	-	-	-	1.084	1.026 ± 1.145	0.004
LCN2 in $\text{ng/mL}$	1.107	1.033-1.185	0.004	-	-	-
ET-1 in $\mu\text{g/mL}$	10.028	0.896-112.196	0.061	2.101	0.887 ± 4.979	0.092

<sup>1</sup>Variable was binarized based on its median value.

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; LCN2: Lipocalin-2; mPAP: Mean pulmonary artery pressure; OR: Odds ratio; PAH: Pulmonary arterial hypertension; SBP: Systolic blood pressure.

**Table 5 Multivariate logistic regression analysis to define the correlation between endothelin-1 concentration and risk for pulmonary arterial hypertension**

Variables	OR (95%CI)	P value
Age in months	0.994 (0.914-1.081)	0.889
Creatinine in $\mu\text{mol/L}$	1.232 (1.056-1.436)	0.008
Diameter in $\text{mm}$	0.984 (0.811-1.195)	0.871
ET-1 in $\mu\text{g/mL}$	9.681 (0.650-144.192)	0.099

ET-1: Endothelin-1; OR: Odds ratio.

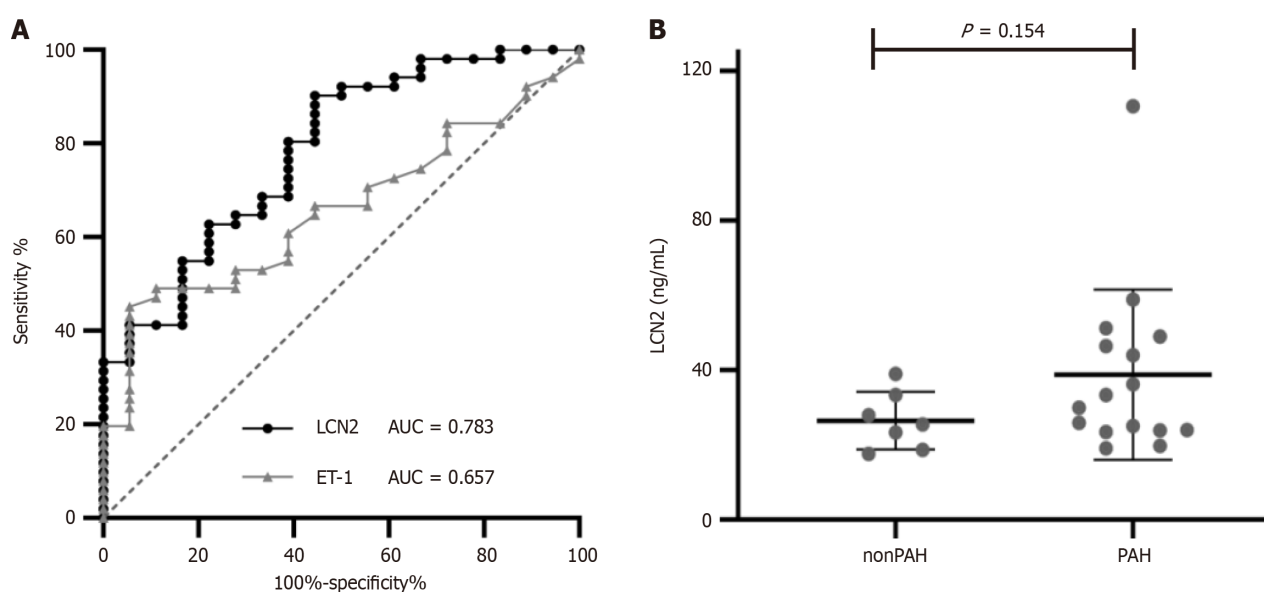
biomarkers that could aid in the evaluation of PAP in this population, ultimately enhancing disease management and patient outcomes.

In the present study, we evaluated the predictive value of LCN2 for PAP in VSD patients. Our findings indicate that the blood level of LCN2 significantly correlates with PAH in VSD patients, as demonstrated through both univariate and multivariate regression analyses. ROC curve analysis reveals that LCN2 has a superior diagnostic value compared to ET-1 (with AUC 0.783 *vs* 0.657). Notably, LCN2 exhibits a sensitivity for diagnosing PAH that exceeds 90% at a cutoff value of 19.42  $\text{ng/mL}$ , making it a valuable tool for screening patients suspected of having PAH. Therefore, for CHD patients with suspected PAH, LCN2 emerges as a crucial reference for estimating PAP and guiding treatment decisions. Conversely, the diagnostic potential of ET-1 for PAH is inferior to LCN2. There is no significant correlation between blood ET-1 concentration and mPAP. In the ROC curve analysis, however, ET-1 demonstrates a high specificity for diagnosing PAH at 94.44%, indicating that it holds utility as a confirmatory marker in the diagnostic evaluation of PAH.

LCN2 is a multifunctional protein that can be up-regulated in diverse pathological processes, including immunological abnormalities, metabolic diseases, and multiple types of tumors[20-22]. In particular, LCN2 is a marker for kidney injury and renal dysfunction, and its concentration significantly increases during both acute and chronic kidney injuries[12-14].

Variables	Adjusted OR (95%CI)	P value
Age of month	0.939 (0.820-1.075)	0.360
Creatinine ( $\mu\text{mol/L}$ )	1.251 (1.050-1.492)	<b>0.012</b>
WBC ( $10^9/\text{L}$ )	1.039 (0.685-1.576)	0.856
Diameter (mm)	1.043 (0.804-1.352)	0.753
LCN2 (ng/mL)	1.150 (1.027-1.288)	<b>0.015</b>

**Figure 1** Multivariate logistic regression analysis the correlation between lipocalin-2 concentration and risk for pulmonary arterial hypertension. LCN2: Lipocalin-2; OR: Odds ratio; WBC: White blood cells.



**Figure 2** Receiver operating characteristic curve and comparison of lipocalin-2 concentration. A: Receiver operating characteristic curve of blood lipocalin-2 (LCN2) and endothelin-1 as predictors for pulmonary arterial hypertension (PAH); B: Comparison of LCN2 concentration between nonPAH and PAH patients after repair surgery. AUC: Area under the receiver operating characteristic curve; ET-1: Endothelin-1.

Given the close functional connection between the heart and kidneys, many CHD patients also exhibit abnormal renal function[23,24]. In the present study, we observed significant differences in renal function between the nonPAH and PAH groups. Additionally, we found that mPAP is significantly correlated with blood creatinine and BUN levels in VSD children. However, it is crucial to determine whether elevated LCN2 levels are primarily due to renal dysfunction or cardiovascular abnormalities. Despite the presence of abnormal renal function in CHD patients, we did not identify any significant correlation between LCN2 blood levels and creatinine or BUN in either univariate or multivariate regression analyses. This finding suggests that the renal abnormalities present are not sufficient to induce a significant increase in LCN2 levels. Consequently, our results imply that increased LCN2 in patients with CHD is more likely associated with PAH-related pathology rather than renal dysfunction. This underscores the potential role of LCN2 as a biomarker specifically linked to PAH in the context of CHD.

Our previous studies, along with recent reports from others, have demonstrated that LCN2 plays a significant role in promoting pulmonary artery smooth muscle cell proliferation and inhibiting apoptosis[8-11]. In our most recent study [25], we highlighted a critical role for LCN2 in glycolytic regulation, which is central to the metabolic theory in PH progression[26,27]. This association may serve as the molecular basis for the correlation between LCN2 and PAH, independent of renal dysfunction that may be present. The multifaceted roles of LCN2 in various physiological and pathological processes[28-30] render it an intriguing molecule for further research and potential therapeutic applications. Delving deeper into the mechanisms through which LCN2 exerts its effects could yield valuable insights not only for the development of new diagnostic tools for PAH but also for enhancing treatment strategies aimed at this challenging condition.

A recent report by Zhang *et al*[31] evaluated the relationship between LCN2 and PH in patients with CHD[31]. However, the types of CHD included in their study were not classified or specified, and they did not take into account the potential impact of renal function on LCN2 levels. While the authors concluded that LCN2 levels are elevated in patients with CHD, they reported a reference value of LCN2 for predicting PH at just 8.1 pg/mL. This value is substantially lower

**Table 6 Predictive values of lipocalin-2 and endothelin-1 for pulmonary arterial hypertension**

	AUC	Youden's index	Sensitivity, %	Specificity, %	Cutoff value
LCN2	0.783	0.4575	90.19	55.56	19.42 ng/mL
ET-1	0.657	0.3954	45.10	94.44	0.39 µg/mL

AUC: Area under the receiver operating characteristic curve; ET-1: Endothelin-1; LCN2: Lipocalin-2.

**Table 7 Correlations of post-repair mean pulmonary artery pressure with clinical variables, *n* = 23**

Variables	Post-operative mPAP		mPAP decrease	
	<i>r</i>	<i>P</i> value	<i>r</i>	<i>P</i> value
Sex, male	0.404	0.056	0.303	0.161
Age in months	0.347	0.105	0.434	0.039
BMI	-0.141	0.531	-0.050	0.826
Creatinine in µmol/L	-0.150	0.493	0.248	0.255
BUN in mmol/L	0.236	0.278	0.411	0.052
Albumin in g/L	0.313	0.156	0.029	0.897
Glucose in mmol/L	-0.045	0.849	-0.057	0.813
Hemoglobin in g/L	0.223	0.306	0.163	0.458
Platelets as 10 <sup>9</sup> /L	-0.066	0.764	0.107	0.628
White blood cells as 10 <sup>9</sup> /L	0.186	0.507	0.623	0.013
SBP in mmHg	0.094	0.677	0.043	0.848
DBP in mmHg	0.361	0.099	0.185	0.410
EF as %	-0.311	0.148	-0.037	0.867
Diameter in mm	0.398	0.060	0.552	0.006
Pre-repair mPAP in mmHg	0.471	0.023	0.883	< 0.001
LCN2 in ng/mL	0.532	0.009	0.181	0.407
ET-1 in µg/mL	0.140	0.523	0.298	0.167

BMI: Body mass index; BUN: Blood urea nitrogen; DBP: Diastolic blood pressure; EF: Ejection fraction; ET-1: Endothelin-1; mPAP: Mean pulmonary artery pressure; SBP: Systolic blood pressure; LCN2: Lipocalin-2.

than our findings, which indicated LCN2 levels of 25 ng/mL[8] in healthy children. Results from other studies reported levels ranging from 0.9 to 5.9 ng/mL or 9.8 to 25.7 ng/mL[32,33]. Compared to the study by Zhang *et al*[31], our research provides more objective and informative results regarding LCN2 Levels in the context of CHD and PH.

In CHD patients with a left-to-right shunt, elevated PAP may not always normalize after the closure of the shunt[1,34]. The reason behind why some CHD patients experience a permanent reversal of PAH following shunt closure, while others continue to exhibit persistent PAH, remain unclear. In our study, we recorded post-repair PAP values for 20 PAH patients; four experienced a reversal of elevated PAP to normal levels, while the remaining patients continued to show signs of PAH. Notably, we found that LCN2 concentration was significantly correlated with post-repair mPAP. Furthermore, patients with post-repair PAH exhibited higher levels of LCN2 compared to non-PAH patients. These findings suggest that blood LCN2 levels could serve as a potential biomarker to indicate whether PAH can be reversed after shunt closure in CHD patients. This highlights the need for future studies with larger sample sizes to further validate LCN2's prognostic value in predicting the outcomes of PAH after surgical intervention. Exploring this relationship could enhance our understanding of PAH in CHD patients and inform clinical decision-making regarding treatment strategies.

### Limitations

This study has some limitations. First, it is a single center cross-sectional study with a relatively small number of research subjects. Future prospective and multicenter studies with larger patient populations will be necessary to enhance the generalizability of the findings. Second, this study focused exclusively on patients with VSD or VSD accompanied by

atrial septal defect, which represent relatively simple types of CHD. Given the diversity of CHD, particularly in children with complex conditions, such as those with segmental PH or a combination of group 1 and group 2 PH, the diagnosis and management of PH must be customized to account for the individual patient's unique anatomical and hemodynamic conditions. Therefore, caution should be exercised when interpreting the results. Third, all patients enrolled in our study underwent right ventricular catheterization. However, most CHD patients with simple lesions typically do not require cardiac catheterization. Consequently, patients who were unwilling or did not require right heart catheterization were excluded from this study, introducing a selection bias. Finally, the determination of post-repair PAH in this study relied on intra-operative ventricular catheterization results obtained after shunt closure. It is important to note that with the cessation of anesthesia and the patient's recovery, the final PAP values may change. This potential bias is challenging to avoid and may impact the interpretation of the results. Addressing these limitations in future research will be crucial for validating the findings and enhancing our understanding of LCN2's role in PAH among CHD patients.

## CONCLUSION

In conclusion, this retrospective study demonstrated that LCN2 blood levels significantly correlate with mPAP in CHD patients. LCN2 has emerged as a candidate biomarker for CHD patients, and its high sensitivity in diagnosing PAH underscores its potential value in patient management.

## FOOTNOTES

**Author contributions:** Wang GL and Liu AJ conceptualized and designed the research; Guo ZK, Bai S and Li XF screened patients and acquired clinical data; Wang GL, Guo ZK, Chen PG, Jiao H and Kong XH performed data curation, visualization, and interpretation; Wang GL, Li YX and Liu AJ wrote the manuscript; Wang GL and Liu AJ performed reviewing and final editing; All authors have read and agreed to the published version of the manuscript. Both Wang GL and Liu AJ have played important and indispensable roles in the experimental design, data interpretation and manuscript preparation as the co-corresponding authors. Wang GL conceptualized, designed, and supervised the project, including literature collection, manuscript submission and revision, with a focus on the association between lipocalin-2 concentration and risk for pulmonary arterial hypertension. Liu AJ played a crucial role in data re-analysis and re-interpretation, figure plotting, comprehensive literature searching, and preparing the final manuscript submission, focusing specifically on the diagnostic value of lipocalin-2 in PAH. The collaboration between Wang GL and Liu AJ was essential to the publication of this manuscript.

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