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Association of nutritional status and laboratory parameters with heart failure among children with congenital heart disease

Hubungan status gizi dan parameter laboratorium dengan gagal jantung pada anak dengan penyakit jantung bawaan

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Abstract

Congenital Heart Disease (CHD) is a structural and functional abnormality of the heart that occurs at birth. If left untreated, CHD can lead to heart failure, respiratory infection, and malnutrition. Data on nutritional status, anemia, leukocyte count, and serum 25-hydroxy vitamin D [25(OH)D] levels in pediatric CHD patients with heart failure remain limited. This study aimed to analyze the correlation between nutritional status, anemia, leukocyte count, and serum 25-Hydroxy vitamin D levels, and heart failure in children with CHD. A cross-sectional study was conducted at three hospitals in Banda Aceh from August 1, 2022, to July 31, 2023. Pediatric patients with CHD underwent anthropometric, echocardiographic, and laboratory examinations. The exclusion criteria included renal, urinary, endocrine, and hematologic-oncological disorders. Data were analyzed using SPSS version 26.0, and the Mann–Whitney U test was applied for nonparametric variables. Results: Of the 128 patients with CHD (46.1% men), 78.9% had heart failure. Poor nutritional status was found in 49.2% of patients, and anemia in 51.6%, with many showing abnormal leukocyte counts and low serum 25(OH)D levels. Low serum 25(OH)D levels (p=0.010; OR=6.7) and abnormal leukocyte counts (p=0.000; OR=55.6) were significantly associated with heart failure. In conclusion, low serum 25(OH)D levels and abnormal leukocyte counts significantly increase the risk of heart failure in children with CHD.

Keywords: Congenital heart disease, heart failure, anemia, leukocytes, vitamin D, nutritional status, children

Abstrak

Penyakit Jantung Bawaan (PJB) merupakan kelainan struktur dan fungsi jantung sejak lahir. Jika tidak ditangani, PJB dapat menyebabkan gagal jantung, infeksi saluran pernapasan, dan malnutrisi. Data mengenai status gizi, anemia, jumlah leukosit, dan kadar 25-hidroksi vitamin D [25(OH)D] serum pada pasien anak dengan PJB yang mengalami gagal jantung masih terbatas. Penelitian ini bertujuan untuk menganalisis hubungan antara status gizi, anemia, jumlah leukosit, dan kadar 25(OH)D serum dengan kejadian gagal jantung pada anak penderita PJB. Penelitian potong lintang ini dilakukan di tiga rumah sakit di Banda Aceh pada 1 Agustus 2022 hingga 31 Juli 2023. Pasien anak dengan PJB menjalani pemeriksaan antropometri, ekokardiografi, dan laboratorium. Kriteria eksklusi meliputi kelainan ginjal, saluran kemih, endokrin, serta gangguan hematologi-onkologi. Analisis data menggunakan SPSS versi 26.0, dengan uji Mann–Whitney U untuk variabel non-parametrik. Hasil, dari 128 pasien PJB (46.1% laki-laki), 78.9% mengalami gagal jantung. Status gizi buruk ditemukan pada 49.2% pasien, anemia pada 51.6%, serta banyak yang menunjukkan jumlah leukosit abnormal dan kadar 25(OH)D rendah. Kadar 25(OH)D rendah (p=0.010; OR=6.7) dan jumlah

leukosit abnormal (p=0.000; OR=55.6) berhubungan signifikan dengan gagal jantung. Kesimpulan**,** kadar 25(OH)D serum yang rendah dan jumlah leukosit abnormal secara signifikan meningkatkan risiko gagal jantung pada anak dengan PJB.

Kata Kunci: Penyakit jantung bawaan, gagal jantung, anak, anemia leukosit, vitamin D, status gizi

Introduction

Congenital Heart Disease (CHD) is the most prevalent structural and functional cardiac anomaly that occurs at birth, affecting approximately 6 to 10 per 1.000 live births globally, with an average incidence of approximately 8 per 1.000 births (Sunaga et al., 2022). The clinical manifestations of CHD vary significantly; some children display critical symptoms early in life, whereas others may remain asymptomatic until adulthood. If not diagnosed and managed effectively, CHD can precipitate serious complications, such as heart failure and malnutrition, which severely impair physical growth and development (Zhang et al., 2023).

Adequate nutrition is paramount for fostering optimal growth and development in children diagnosed with CHD, necessitating vigilant monitoring throughout childhood and adolescence (Zhang & Lü, 2021). Malnutrition in this demographic is complex and can result from myriad factors, including prenatal influences and genetic predispositions, heightened metabolic demands, poor oxygenation, and inadequate nutrient intake or absorption (Blasquez et al., 2016; Mir et al., 2019). These issues can be further exacerbated by various conditions, such as chronic hypoxemia, dyspnea, recurrent vomiting, and respiratory infections, all of which may limit nutritional utilization and amplify underlying deficiencies (Kato et al., 2020).

In addition to deficiencies in macronutrients, the insufficiency of vital micronutrients presents a significant concern among pediatric heart failure patients, particularly with regard to vitamin D levels. A considerable proportion of individuals with chronic heart failure display deficiencies in essential vitamins, including A, calcium, magnesium, and vitamin D, with Studies have indicated that many children with CHD exhibit reduced serum levels of 25-hydroxyvitamin D compared to healthy controls (Chang et al., 2016). Maternal vitamin D levels undergo a two- to three-fold increase during early gestation, underscoring its critical role in embryonic cardiogenesis, particularly during weeks 2–7 of fetal development (Salehi et al., 2020; Zhou & Qian, 2018).

The current literature highlights the intersection of malnutrition and heart failure among children with CHD, where deficiencies in both macro-and micronutrients are prominent (Billingsley et al., 2020; Zhang & Lü, 2021). Multiple studies across Europe and North America have indicated that vitamin D deficiency is prevalent among patients with chronic heart failure, including pediatric patients with congenital heart disease (CHD) (Gökalp et al., 2022; Hao & Chen, 2019; Roffe-Vazquez et al., 2019). Research has shown that Diminished levels of 25-hydroxyvitamin D (25(OH)D) negatively correlate with heart failure outcomes. In China, a significant association has been found between low vitamin D levels and exacerbation of heart failure symptoms (Hao & Chen, 2019; Roffe-Vazquez et al., 2019), and similar findings have been reported in studies across various demographics in the United States (Özdemir, 2020; Gökalp et al., 2022). The pattern of vitamin D deficiency extends to pediatric populations, with studies indicating that a notable proportion of children with recurrent wheezing, a condition that can share similar pathophysiological characteristics with cardiac conditions, also exhibit significant vitamin D deficiency (Doğru & Seren, 2017).

Despite the global acknowledgment of the protective role of vitamin D in maintaining cardiovascular and immune health, there remains a dearth of data, particularly in low- and middle-income countries such as Indonesia (Al Rahmad, 2023; Oktaria et al., 2022). The lack of localized studies hampers the understanding of the relationship between nutritional status, anemia, and immune response, measured through leukocyte counts and serum vitamin D levels in pediatric heart failure cases associated with CHD (Düğeroğlu & Kaya, 2022; Roffe-Vazquez et al., 2019). Without comprehensive epidemiological data, healthcare providers in

these regions face challenges in implementing timely and effective interventions, leading to suboptimal management of heart failure in children (Rastegar et al., 2024). Limited access to detailed metabolic and immunological evaluations further exacerbates these challenges, restricting the effectiveness of evidence-based practice (Düğeroğlu & Kaya, 2022; Izumi et al., 2016).

Consequently, this study aimed to explore the associations between nutritional status, anemia, leukocyte counts, serum 25-hydroxy vitamin D levels, and the incidence of heart failure in children diagnosed with congenital heart disease.

By addressing this critical research gap, this study provides new insights into the predictive role of serum 25(OH)D and immune markers in the pathogenesis of heart failure in CHD. Furthermore, it highlights the essential nature of assessing nutritional and micronutrient status as integral components of standard care protocols in pediatric cardiology.

Methods

This was an analytical observational study with a retrospective approach, utilizing secondary data from pediatric patients diagnosed with congenital heart disease (CHD) who were hospitalized during the study period at the hospital. This study was conducted at three referral hospitals in Banda Aceh, Indonesia: Dr. Zainoel Abidin General Hospital (RSUZA), Harapan Bunda Hospital (RSHB), and Mother and Child Hospital (RSIA). Data collection was conducted from August 1, 2022, to July 31, 2023.

The study population comprised all pediatric patients diagnosed with CHD who were admitted to the three hospitals. The inclusion criteria were complete clinical and laboratory data related to the variables of interest. Exclusion criteria were Children with renal or urinary tract disorders, endocrine abnormalities, or hematologic-oncologic diseases were excluded.

Data were retrieved from medical records and included variables such as sex, age, body weight, height, nutritional status, CHD type, number of defects, laboratory values (hemoglobin level, leukocyte count, and serum 25-Hydroxy vitamin D), and heart failure status based on the NYHA and Ross classification. The diagnosis of CHD was confirmed by a pediatric cardiologist using echocardiography.

Serum 25-Hydroxy vitamin D [25(OH)D] levels were measured using an immunoenzymatically assay with IDS OCTEIA reagent. Vitamin D status was categorized as normal (30–100 ng/mL) or abnormal, including insufficiency (21–29 ng/mL), deficiency (<20 ng/mL), and severe deficiency (<5 ng/mL). Hemoglobin and leukocyte levels were assessed using flow cytometry analysis. Anemia was defined as a hemoglobin level of <11 g/dL, based on WHO guidelines. Leukocyte counts were considered abnormal if they were outside the range of 5.000–10.000 cells/μL. Nutritional status was assessed using anthropometric indices plotted against age-based CDC and WHO growth charts.

Data were analyzed using SPSS version 26.0. Normality was assessed using the Kolmogorov-Smirnov test. The Mann-Whitney U test was used to compare non-normally distributed variables, and Fisher's exact test was used to assess the associations between categorical variables. Statistical significance was set at $p \leq 0.05$.

This study was approved by the Health Research Ethics Committee of the Faculty of Medicine at Universitas Syiah Kuala/dr. Zainoel Abidin Hospital, Banda Aceh (No. 225/EA/FK-RSUDZA/2021, July 28, 2021). Informed consent was obtained from the parents or legal guardians prior to blood and data collection.

Result and Discussion

A total of 128 children diagnosed with congenital heart disease (CHD) were included in this study. Of these, 59 (46.1%) were men and 69 (53.9%) were women. The mean age was 16.9 months (SD ± 26.0), with a median age of 4 months (range, 1–112 months).

Among the participants (51.6%) had a single cardiac defect (42.1%) had two defects, and 6.3% had three defects. A total of children (78.9%) presented with heart failure. Nutritional status assessment showed that 49.2% of the children were severely malnourished, 29.7% were moderately malnourished, 20.3% had a normal nutritional status, and only one (0.8%) was overweight. Anemia was observed in 51.6% of the subjects.

Laboratory results showed that 51.6% of the children had hemoglobin levels below 11 g/dL, with a mean Hb of 12.6 g/dL and a range of 4.6–23.7 g/dL. Leukocytosis or leukopenia was detected in 92 patients (71.9%), with a mean leukocyte count of 11.6 × 10^3/µL (range: 2.2 – 26.7 × 10^3/µL). Regarding serum 25-hydroxyvitamin D [25(OH)D] levels, only 23 children (18.0%) had normal levels (≥30 ng/mL). The remaining 82.0% of children had insufficient or deficient vitamin D levels, with a median concentration of 17.9 ng/mL (range: 3.4 – 185 ng/mL).

Table 1. Characteristics of children with Congenital Heart Disease (CHD) (n = 128)

Variable	Category	n (%) or Value	Additional Notes
Sex	Male	59 (46.1)	
	Female	69 (53.9)	
Age (months)	Mean ± SD	16.9 ± 26.0	
	Median (Range)	4 (1–112)	
Number of Cardiac Defects	1 defect	66 (51.6)	
	2 defects	54 (42.1)	
	3 defects	8 (6.3)	
Heart Failure	Present	101 (78.9)	Based on NYHA/Ross criteria
	Absent	27 (21.1)	
Nutritional Status	Severely malnourished	63 (49.2)	Based on WHO/CDC standards
	Moderately malnourished	38 (29.7)	
	Normal nutrition	26 (20.3)	
	Overweight	1 (0.8)	
Anemia (Hb <11 g/dL)	Yes	66 (51.6)	Mean Hb: 12.6 g/dL (Range: 4.6–23.7)
	No	62 (48.4)	
Leukocyte Count (/µL)	Normal (5.000–10.000)	36 (28.1)	Mean: 11.6 ×10^3/µL (Range: 2.2–26.7)
	Abnormal (<5.000 or >10.000)	92 (71.9)	
25-Hydroxyvitamin D [25(OH)D] (ng/mL)	Normal (≥30)	23 (18.0)	Median: 17.9 (Range: 3.4–185)
	Abnormal (<30)	105 (82.0)	Includes insufficiency and deficiency

Table 2. Factors associated with heart failure in CHD patients

Variable	Bivariate Analysis		Multivariate Analysis	
	Odds Ratio (OR)	p-value	Odds Ratio (OR)	p-value
Anemia	1.05	0.690		
Nutritional status	1.25	0.030	1.56	0.540
Leukocyte count	1.69	<0.001	52.8	<0.001
25(OH)D serum level	1.53	<0.001	5.62	0.020

Bivariate analysis using Fisher's exact test (Table 2) revealed statistically significant associations between several variables and the presence of heart failure in children with congenital heart disease (CHD). Specifically, nutritional status, leukocyte count, and serum 25-hydroxyvitamin D [25(OH)D] levels were significantly associated with heart failure (p = 0.03, <0.001, respectively). These findings suggest that children with poor nutritional status, abnormal leukocyte counts, and suboptimal vitamin D levels are more likely to develop heart failure.

The odds ratio (OR) for nutritional status was 1.25, indicating that children with poor nutritional status had a 25% higher likelihood of developing heart failure than their well-nourished counterparts. Although modest, this association was statistically significant, supporting the role of nutritional deficiency as a contributing factor in the cardiac decompensation. For leukocyte count, the OR was 1.69, indicating a 69% increased likelihood of heart failure in children with abnormal leukocyte levels. This strong association may

reflect the role of systemic inflammation or underlying infections that exacerbate heart failure in pediatric patients with CHD.

The OR for serum 25(OH)D levels was 1.53, suggesting that children with insufficient or deficient vitamin D levels were 53% more likely to develop heart failure. This aligns with previous studies showing that vitamin D plays a key role in cardiovascular regulation, myocardial function and inflammatory modulation. Conversely, anemia was not significantly associated with heart failure in this population ($p = 0.69$), and an OR of 1.05 indicated only a minimal difference in risk between anemic and non-anemic participants. This result may be due to the complex and multifactorial nature of anemia in patients with CHD, in which compensatory mechanisms can mask its clinical impact on heart failure status.

Multivariate logistic regression analysis (Table 2) identified leukocyte count and serum 25-hydroxyvitamin D [25(OH)D] levels as independent predictors of heart failure in children with congenital heart disease (CHD). Abnormal leukocyte counts were strongly associated with heart failure (OR = 52.8, $p < 0.001$), indicating that children with elevated or dysregulated leukocyte levels were > 50 times more likely to develop heart failure than those with normal leukocyte levels. This finding suggests a critical role for systemic inflammation or underlying infection in the pathophysiology of cardiac dysfunction in children with CHD. Additionally, low serum 25(OH)D levels were significantly associated with heart failure (OR = 5.62, $p = 0.020$), implying that vitamin D deficiency may increase the risk of heart failure by more than fivefold. This result reinforces the evidence of the involvement of vitamin D in cardiovascular function and myocardial regulation. In contrast, nutritional status did not emerge as a significant predictor in the multivariate model (OR = 1.56, $p = 0.540$), suggesting that while malnutrition may be associated with heart failure in the univariate analysis, its predictive effect diminishes when controlling for inflammatory and micronutrient factors. Overall, these findings highlight the importance of routinely monitoring leukocyte levels and vitamin D status as part of an integrated approach to heart failure risk assessment in children with CHD.

This study found a high prevalence of heart failure (78.9%) among children with congenital heart disease, consistent with prior evidence that CHD is the leading cause of pediatric heart failure (Hinton & Ware, 2017). Although more females than males were affected in this study, sex differences in CHD prevalence vary by region and subtype (Yandika et al., 2025; Umboh et al., 2022).

Most participants were infants with a median age of 4 months, suggesting that many CHD cases were diagnosed relatively early. However, early diagnosis is critical for improving patient outcomes. Delays in detection can lead to complications, including malnutrition and decompensated heart failure (Dhina, 2023).

More than 49% of the participants were severely malnourished. Malnutrition in CHD is attributed to increased metabolic demand, poor oral intake, hypoxia, and inefficient nutrient absorption (Umboh et al., 2022; Blasquez et al., 2016). These findings are consistent with those of other Indonesian studies that reported significant associations between cyanotic CHD and poor nutritional status (Putri & Ariwibowo, 2023; Adinda et al., 2018).

Anemia was present in more than half of the participants. In CHD, especially cyanotic types, compensatory erythropoiesis may mask the underlying iron deficiency, leading to misleadingly normal Hb levels despite impaired oxygen delivery (Wray & Sensky, 2011). Although common, anemia was not statistically associated with heart failure in this study ($p = 0.69$), potentially because of the complex pathophysiology involving the compensatory mechanisms.

Leukocytosis or leukopenia was observed in 71.9% of the patients. Elevated or decreased white blood cell counts in patients with CHD may reflect subclinical infections or immune dysfunction due to altered pulmonary circulation, consistent with previous studies (Owayed et al., 2000). Leukocyte count was strongly associated with heart failure in both bivariate ($p < 0.001$; OR = 1.69) and multivariate analyses ($p < 0.001$; OR = 52.8), highlighting its potential as a prognostic factor.

Serum 25(OH)D deficiency was detected in 82% of the children, with a median level far below the recommended threshold of 30 ng/mL. Vitamin D plays a crucial role in cardiovascular health by modulating the myocardial function and systemic inflammation. Its deficiency has been associated with poor outcomes in patients

with heart failure (Lee et al., 2008; Wang et al., 2012). In this study, low vitamin D levels were independently associated with heart failure ($p = 0.020$; OR = 5.62), underscoring their potential role in the risk stratification and management of heart failure.

These findings reinforce the multifactorial etiology of heart failure in CHD and emphasize the importance of integrating nutritional and biochemical monitoring into standard pediatric cardiac care protocols. The limitations of this study include its retrospective design and the potential for residual confounding. Future prospective studies are needed to confirm causality and evaluate interventions targeting vitamin D and immune markers.

Model for Predicting Heart Failure in Children With CHD

This study evaluated the association between nutritional status, anemia, leukocyte count, serum 25-hydroxyvitamin D (25(OH)D) levels, and heart failure in pediatric patients with congenital heart disease (CHD). Multivariate logistic regression analysis revealed that low 25(OH)D levels and abnormal leukocyte counts were independent predictors of heart failure in this population. These findings support the existing literature emphasizing the critical roles of systemic inflammation and immune activation in the progression of heart failure in children with CHD (Amdani et al., 2024; Gilljam et al., 2019).

Elevated leukocyte counts may indicate ongoing infections, such as recurrent respiratory tract infections, which are prevalent in children with hemodynamically significant CHD due to pulmonary overcirculation or diminished immune function (Mignot et al., 2023). Inflammatory processes can exacerbate myocardial remodeling and endothelial dysfunction and contribute to declining ventricular performance, particularly in the pediatric population with structural heart defects (Amelia et al., 2020). Hence, the leukocyte count may serve as a practical clinical marker for identifying children at an elevated risk of decompensation and heart failure (Yousafzai et al., 2024).

Additionally, our study confirmed a significant association between serum 25(OH)D deficiency and heart failure. D's regulatory functions of vitamin D in calcium homeostasis and immune modulation are crucial in the context of heart failure, and deficiencies have been implicated in ventricular hypertrophy and increased inflammation, both of which contribute to pathogenesis (Marino et al., 2020). This aligns with previous studies highlighting that children with CHD often present significantly lower serum 25(OH)D levels than their healthy peers, reinforcing the need for routine serum 25(OH)D screening and supplementation in this high-risk group (Alverina et al., 2022; Fedora et al., 2019).

Regarding nutritional status and its relationship with heart failure, our investigation found that while malnutrition was associated with heart failure, it was not a significant predictor in the adjusted model. This suggests that confounding factors such as inflammation and deficiencies in key micronutrients may be involved (Algharyani et al., 2021; Yousafzai et al., 2024). Malnutrition, often a result of factors such as increased metabolic demands, poor dietary intake, and gastrointestinal malabsorption, frequently coexists with CHD (Amelia et al., 2020; Salwaa et al., 2022). This complexity may obscure the direct impact of malnutrition on the risk of heart failure.

Anemia was not significantly correlated with heart failure in our study. Previous research has proposed anemia as a potential exacerbating factor in pediatric heart failure; however, our results indicate that hemoglobin levels alone might not effectively predict cardiac dysfunction in this patient group (Oyarzún et al., 2018). The compensatory erythropoietic response frequently observed in cyanotic CHD may further mask the direct effects of anemia on heart failure status (Amdani et al., 2024). Notably, our findings highlight the need for a more nuanced approach to evaluate the various interactions among nutritional status, inflammatory markers, and micronutrient levels in relation to heart failure in children with CHD.

Overall, the findings of this study underscore the clinical relevance of monitoring leukocyte counts and vitamin D status as actionable markers for the management of heart failure risk in pediatric patients with congenital heart disease. Integrating the assessment of inflammatory and micronutrient parameters into standard clinical protocols could improve risk stratification, enhance early detection, and inform intervention strategies in pediatric cardiology settings.

This study was limited by its retrospective design and reliance on single-center data from hospitalized patients, which may not fully represent the broader population of children with CHD. Moreover, causality cannot be inferred, and potential confounders, such as specific types of CHD, medication use, and socioeconomic factors, were not fully controlled. Prospective multicenter studies with larger and more diverse cohorts are needed to validate these findings and explore the mechanistic pathways linking inflammation and vitamin D status to heart failure in pediatric CHD.

Conclusion

This study demonstrated that abnormal leukocyte counts and low serum 25-hydroxyvitamin D [25(OH)D] levels were significantly associated with heart failure in children with congenital heart disease (CHD). These two variables remained independent predictors in the multivariate analysis, highlighting their potential as clinical markers for the early identification of high-risk patients. Although malnutrition and anemia were prevalent in the study population, they did not independently predict heart failure after adjusting for confounding variables. These findings emphasize the multifactorial nature of cardiac decompensation in pediatric CHD and the need to focus on inflammatory and micronutrient status as part of comprehensive cardiac risk assessment strategies.

Routine monitoring of leukocyte counts and serum 25(OH)D levels should be integrated into the clinical management of children with CHD to support the early detection and prevention of heart failure. Vitamin D supplementation may be considered a preventive or adjunctive therapeutic measure, particularly in patients with documented deficiencies. Pediatric cardiology teams should adopt a multidisciplinary approach that includes nutritional surveillance, infection control, and optimizing micronutrient levels. Future studies should explore the effects of correcting vitamin D deficiency and managing systemic inflammation on HF progression and outcomes of heart failure in this population. These efforts can contribute to more personalized and effective care strategies for children with heart disease.

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