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Correlation of Serum Ferritin with Hematocrit in Children Infected with Dengue

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Background: Dengue infection is a major global health concern in tropical and subtropical regions, especially among children, ranging from mild to severe disease with high morbidity and mortality. Although ferritin and hematocrit have prognostic value individually, their correlation in pediatric dengue remains underexplored. This study was conducted to determine the correlation between serum ferritin and hematocrit levels in children with dengue infection.

Materials and methods: This cross-sectional study included 69 children with dengue infection. Data collected included age, sex, nutritional status, disease severity, and hematologic parameters. Blood samples were obtained from all participants, serum ferritin levels were measured using Chemiluminescent Microparticle Immunoassay (CMIA), while hematocrit was measured from whole blood using an automated hematology analyzer. Correlation was assessed using Pearson's or Spearman's rho test, followed by multiple linear regression analysis.

Results: The mean age was 10.09 ± 4.23 years old, with 52.2% male and 47.8% female participants. Nutritional status was 29% undernourished, 58% normal, and 13% overnourished. Mild dengue was observed (65.2%), while 34.8% had severe disease. The mean serum ferritin level was 4820.97 ± 6327.75 ng/mL, and the mean hematocrit was $42.10 \pm 6.21\%$. Spearman's Rho test showed significant moderate positive correlation between serum ferritin and hematocrit. Multiple linear regression analysis demonstrated that increased serum ferritin levels were significantly correlated with an increased hematocrit levels, whereas age, gender, nutritional status, and disease severity were not significantly associated.

Conclusion: Serum ferritin levels were positively correlated with serum hematocrit levels in children infected with dengue, suggesting a potential role for ferritin as both an inflammatory marker and an indicator of hemoconcentration for early risk stratification.

Keywords: dengue, ferritin, hematocrit, children

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Introduction

Dengue fever was a global health issue, particularly in tropical and subtropical regions. According to the World Health Organization (WHO), dengue infection is caused by a virus transmitted through mosquito bites, with an estimated 390 million infections occurring annually, of which 96 million manifested significant clinical symptoms.^{1,2} The clinical spectrum ranged from asymptomatic infection to dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), resulting in high morbidity and mortality in the pediatric population. Furthermore, children represent an especially important population in dengue research because they are more susceptible to rapid plasma leakage, hemodynamic instability, and progression to shock. At the same time, age-related differences in immune response and intravascular volume may also affect disease presentation and severity assessment.³

After an incubation period of 4–10 days, dengue infection typically presents suddenly with a febrile phase lasting 2–7 days, which is characterized by high fever, headache, retro-orbital pain, muscle and joint pain, nausea, vomiting, and rash.⁴ Some cases progress to the critical phase, involving plasma leakage, which can lead to DHF and DSS through hemorrhagic manifestations, thrombocytopenia, and increased vascular permeability.⁵ Early identification of severe dengue was crucial for improving treatment outcomes and reducing mortality, especially in children who were more vulnerable due to their immature immune systems and limited blood volume. Differentiating between mild and severe dengue at an early stage was also challenging due to overlapping symptoms and the absence of specific markers.⁶ From the perspective of diagnosis and prognosis of dengue infection, several markers or biomarkers, including routine hematologic parameters, liver enzymes, and pro-inflammatory cytokines, have been studied. However, their diagnostic performance remains limited.⁷

Serum ferritin, an acute-phase reactant and iron storage marker, was reported to increase significantly during infection in response to inflammation and immune activation. High ferritin levels (>1,200 ng/mL) have been associated with DHF and DSS events and correlated with CRP and platelets, making it a potential early biomarker for disease progression.^{8,9} Hematocrit reflected the volume of red blood cells, played a role as an indicator of plasma

leakage during the critical phase of dengue, especially in children.^{10,11} Hematocrit changes tended to be temporary and were influenced by fluid dynamics.¹² Although both biomarkers have prognostic value, no study has yet evaluated the correlation between serum ferritin levels and hematocrit using a linear analytical approach in pediatric dengue. Ferritin reflects the intensity of the inflammatory response and tissue damage, while hematocrit is influenced by fluid volume. Both may provide complementary information for risk stratification and clinical management of dengue in children. Therefore, this study was conducted to evaluate the relationship between serum ferritin levels and hematocrit in pediatric patients with dengue infection.

Materials and methods

Subject Selection and Study Setting

Pediatric patients with a diagnosis of dengue infection, age ≤ 18 years, were included in the study. Meanwhile, patients with congenital heart disease, chronic kidney disease, immunosuppressive conditions, anemia, and other hematologic diseases were excluded. The study was performed at Ngoerah General Hospital, Denpasar, from August to December 2024. Dengue infection was defined based on clinical diagnosis by identification of typical symptoms (fever, rash, muscle pain) and laboratory serological tests (NS1 antigen, IgM/IgG dengue) in accordance with WHO criteria. The sample size was calculated based on the minimum sample requirement for a correlation study using an expected correlation coefficient of $r=0.5$, resulting in a minimum of 57 participants. The Research Ethics Committee has approved the study protocol, details of the ethical approval are stated in the Ethical Statement.

Demographic and Health Records

After subject selection, subject demographic and health records (age, sex, nutritional status, and disease severity) were obtained based on clinical and laboratory examinations of dengue infection, anamnesis, and physical examination. Both nutritional status (malnutrition, good nutrition, or overnutrition) and disease severity (mild or severe) were categorized according to WHO criteria.

Hematocrit Measurement

Isolates whole blood samples were collected from all participants for analysis. Hematocrit levels were then measured using an automated hematology analyzer. The results were reported as percentages (%).

Chemiluminescent Microparticle Immunoassay (CMIA) for Serum Ferritin

Collected blood was processed to obtain serum by centrifugation at 15,000 RPM for 15 minutes. The resulted serum layer was carefully separated from the cellular components and stored at -80°C. Serum ferritin was measured with Alinity i Ferritin Reagent Kit (Cat# 07P65 G71320R03 B7P650, Abbott, Chicago, IL, USA). Briefly, the kit was a 2-step immunoassay to quantify ferritin in human serum using CMIA technology. Serum containing Ferritin and anti-ferritin-coated paramagnetic microparticles were combined. An anti-ferritin acridinium-labeled conjugate was added to create a reaction mixture. The resulting chemiluminescent reaction was measured as relative light units (RLUs). With the ARCHITECT i System (Abbot), the results can be obtained and converted into ng/mL.

Results

Subject Characteristics

A total of 69 subjects were included with an average age of 10.09 years (Table 1). The distribution of gender showed a relatively balanced proportion. Most of the subjects had good nutritional status (58%) and mild disease severity (65.2%). The average serum ferritin level was 4820.97±6327.75 ng/mL, and the average hematocrit level was 42.10±6.21 %

Correlation Between Serum Ferritin and Hematocrit Levels

Bivariate correlation analysis using Spearman's Rho test for serum ferritin and hematocrit levels showed a correlation coefficient (r) of 0.543 and a p-value of <0.001 (Table 2). This indicated that an increase in serum ferritin levels was significantly and moderately correlated with an increase in hematocrit levels in pediatric dengue subjects (Figure 1).

Expression Multiple Linear Regression Analysis of Serum Ferritin Level, Age, Gender, Nutritional Status, and

Disease Severity with Hematocrit Level as the Dependent Variable

The analysis results showed that serum ferritin level had a β coefficient of 0.210, with an R^2 value of 0.236 and a p-value of 0.006, indicating that serum ferritin level was significantly correlated with hematocrit level. Thus, every increase of 1 ng/mL in serum ferritin was associated with a 0.236% increase in hematocrit level. However, age, gender, nutritional status, and disease severity did not show significant correlations with hematocrit level (Table 3).

Discussion

In this study, the averages of serum ferritin levels of dengue-infected subjects were higher than the normal serum ferritin level. This increase supported the role of ferritin as a marker of acute inflammation and disease severity in dengue infection. Beyond its role in infectious diseases, ferritin has also been recognized as a clinically relevant biomarker in other conditions, including cancer, where it is often used in combination with other markers to improve diagnostic accuracy.¹³ The present data were consistent with a previous

Table 1. Subject characteristics (n=69).

| Variable | n (%) |
|--|-----------------------|
| Age (Mean \pm SD) (years) | 10.09 \pm 4.23 |
| Gender | |
| Male | 36 (52.2) |
| Female | 33 (47.8) |
| Nutritional Status | |
| Malnutrition | 20 (29) |
| Good nutrition | 40 (58) |
| Overnutrition | 9 (13) |
| Disease Severity | |
| Mild | 45 (65.2) |
| Severe | 24 (34.8) |
| Serum ferritin level (ng/mL) (Mean \pm SD) | 4820.97 \pm 6327.75 |
| Hematocrit level (%) (Mean \pm SD) | 42.10 \pm 6.21 |

Table 2. Correlation between serum ferritin and hematocrit levels.

| Variable | Mean ± SD | Correlation Coefficient (r) | p-Value |
|----------------------|-------------------|-----------------------------|---------|
| Serum ferritin level | 4820.97 ± 6327.75 | 0.543 | <0.001* |
| Hematocrit level | 42.10 ± 6.21 | | |

*Significant statistically ($p < 0.05$; two-tailed) using Spearman's Rho test.

study, which reported a significant increase in ferritin levels in children with severe dengue compared to those with mild dengue.¹⁴ Ferritin did not serve as an inflammation marker merely, but also reflected macrophage activation and an excessive immune response to dengue virus infection, which could trigger macrophage activation syndrome (MAS) and hyperferritinemia.⁹ Furthermore, high ferritin levels correlated with severe thrombocytopenia and hemorrhagic manifestations, making ferritin a potential biomarker for dengue severity.¹⁵

This study found a relatively balanced distribution between male and female subjects, making it unlikely that sex distribution acted as a significant bias. However, the pattern reflected that more boys than girls suffered from dengue infection, which aligned with findings in Venezuela, which reported a slightly higher proportion of males among children with dengue infection.¹⁶ This supported the hypothesis that boys generally had a slightly higher risk of contracting dengue, possibly related to behavioral

factors, environmental exposure, or biologically different immune responses. Similarly, in a meta-analysis on dengue hemophagocytic syndrome (DHS), the gender distribution showed a male predominance, with 58.6% males and 41.4% females among 167 analyzed cases, which also supported this study's findings.¹⁷

In this study, the distribution of nutritional status among pediatric patients with dengue infection showed that the majority of patients were categorized as having good nutritional status, followed by those with malnutrition and overnutrition. These findings were consistent with other studies, which found increased serum ferritin levels in dengue patients. In that study, elevated ferritin levels were often associated with greater disease severity, suggesting that the patient's nutritional condition could influence disease progression.¹⁶

Another study found a significant increase in serum ferritin levels in children with dengue, particularly in those suffering from severe infections. Ferritin, as an acute-

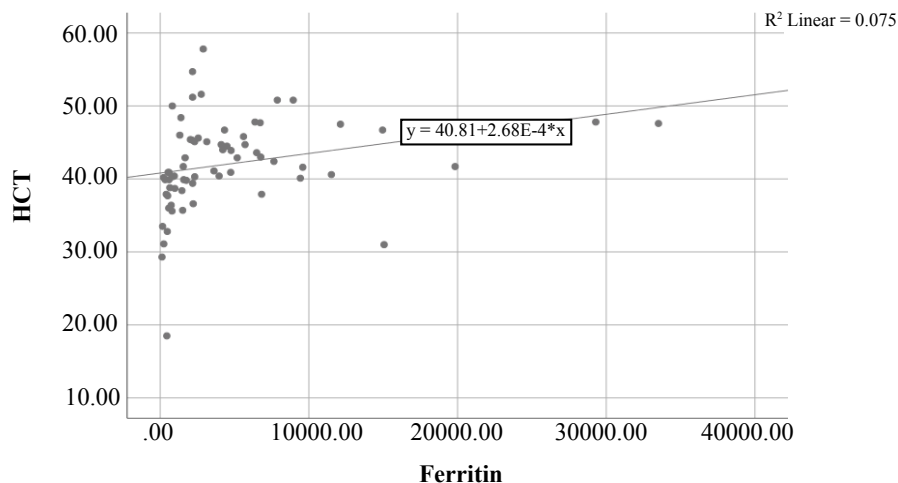


Figure 2. Scatter plot of ferritin levels and serum hematocrit.

Table 3. Multiple linear regression analysis of serum ferritin level, age, gender, nutritional status, and disease severity with hematocrit level as the dependent variable.

| Variable | B | SE | Coefficient β | R ² | p-Value |
|----------------------|--------|-------|---------------------|----------------|---------|
| Serum ferritin level | 0.000 | 0.000 | 0.210 | 0.236 | 0.006* |
| Age | 0.503 | 0.177 | 0.343 | | 0.082 |
| Gender | -0.435 | 1.439 | -0.035 | | 0.763 |
| Nutritional Status | 1.530 | 1.116 | 0.156 | | 0.175 |
| Disease Severity | -2.493 | 1.585 | -0.193 | | 0.121 |
| Constant | 36.580 | 2.391 | | | |

*Statistically significant ($p < 0.05$) using linear regression test.

phase protein, increased in response to inflammation, and in patients with dengue, markedly elevated ferritin levels were often associated with severe inflammatory syndromes. The main difference lay in the higher average ferritin levels observed in this study (4820.97 ng/mL) compared to other which may have been attributable to differences in patient population characteristics or the stage of disease severity at the time of sampling.¹⁶

From the perspective of hematocrit levels, the results of this study demonstrated a relatively normal average (42.10%), although slightly lower than the standard hematocrit range for healthy children. Hematocrit reflects the proportion of red blood cells relative to total blood volume, and its level is closely influenced by red blood cell production and plasma volume.¹⁷ This might have reflected changes in blood volume and hydration due to plasma leakage, a common feature of dengue infection. A study confirmed that in more severe dengue infections, changes in hematocrit were often more pronounced, with a sharper decrease attributed to bleeding or extensive plasma leakage. In the current study, the slightly reduced hematocrit levels could suggest that most patients were still in the early stages of illness and had not progressed to the more severe phase characterized by shock or significant hematocrit decline.¹⁴

The differences between the results of this study and those of several other studies could be explained by factors such as variations in research design, sample size, or demographic characteristics of the patient populations. For instance, a study that evaluated the relationship between nutritional status and the occurrence of dengue

shock syndrome (DSS), it was found that children with poor nutritional status tended to have lower ferritin and hematocrit levels, indicating the role of nutritional condition in influencing the clinical outcomes of dengue infection. This suggested that nutritional status and related factors, such as hydration and disease severity, could significantly affect both ferritin and hematocrit levels.¹⁹

The findings of this study demonstrated a significant positive correlation between serum ferritin levels and hematocrit levels in children with dengue infection. A study also observed a significant increase in ferritin levels in children with dengue, emphasizing ferritin as a marker of acute inflammation and a mediator of oxidative stress. These findings reinforced the hypothesis that hyperinflammation is a central feature of severe dengue infection.¹⁶ A study highlighted the association between ferritin and IL-18, they did not specifically explore its correlation with hematocrit. The present study provided evidence that ferritin levels were not only reflective of inflammation but also correlated with hemodynamic changes, such as hemoconcentration, evident in the increased hematocrit levels.¹⁶ These findings were also aligned with other studies, which identified hyperferritinemia as an important indicator of severe dengue. Their study reported that ferritin levels exceeding 5000 ng/mL were often correlated with clinical severity, including the risk of plasma leakage that contributed to elevated hematocrit levels.^{14,15,20}

In a sepsis condition, the patient showed that elevated ferritin levels were associated with increased mortality and heightened systemic inflammation, but did not specifically

address the relationship between ferritin and hematocrit. These findings indicated that although ferritin served as a general marker of inflammation, its correlation with hematocrit was context-dependent and strongly influenced by the nature of the disease.¹⁹ Meanwhile, other study reported a relationship between ferritin and hemoglobin levels in a population of adolescents.²¹ Although their findings were not directly relevant to acute inflammation or dengue infection, they provided additional insight into ferritin's association with erythropoiesis status. Taken together, the differences and similarities between the current findings and those of previous studies appeared to be influenced by a variety of factors, including differences in study populations (children vs. adults), clinical conditions (acute dengue vs sepsis or DHS), and disease phases (viremic, critical, or recovery). The positive correlation between ferritin and hematocrit observed in this study most likely reflected an acute inflammatory response and plasma leakage that resulted in hemoconcentration during the critical phase of dengue, distinct from conditions like DHS, which typically resulted in cytopenia due to excessive macrophage activation.²²

This study had several limitations. Potential confounding factors, such as environmental or socioeconomic factors, that might have influenced serum ferritin and hematocrit levels in children with dengue infection were not analyzed. Additionally, the data were obtained from a single hospital setting, which may have introduced selection bias and limited the generalizability of the findings to broader pediatric populations.

Serum ferritin levels were positively correlated with hematocrit levels in children infected with dengue. Further research was recommended involving multiple healthcare centers to ensure that the results would be more representative and provide a more comprehensive understanding of the relationship between serum ferritin and hematocrit levels in children infected with dengue. Future studies are also recommended to evaluate serial ferritin and hematocrit measurements throughout the clinical course of dengue and to assess their potential utility as combined markers for early severity stratification in pediatric patients. Clinically, serum ferritin may be considered as an adjunctive parameter alongside hematocrit and routine clinical assessment to support early identification of children at risk of disease

progression, particularly in settings where close monitoring of plasma leakage and inflammatory burden is needed.

Conclusion

This study demonstrated a significant moderate positive correlation between serum ferritin and hematocrit levels in children with dengue infection. Increased ferritin levels were consistently associated with higher hematocrit values, suggesting a link between inflammatory response and hemoconcentration. Moreover, serum ferritin remained an independent predictor of hematocrit levels after adjusting for potential confounding variables. These findings highlight the potential utility of ferritin as a complementary biomarker in evaluating disease progression in pediatric dengue. Incorporating serum ferritin into clinical assessment may support early risk stratification and improve patient management.

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Authors' Contributions

NBH contributed to the research, conception/design, and data acquisition. MYD was responsible for data analysis and result interpretation. PAS contributed to manuscript preparation as well as figure and/or table design. IWG, IBG, DKW, DLU, SPS, and MYS were involved in the critical revision of the manuscript. All authors have read and approved the final version of the manuscript.

Ethical Statement

This study was approved by the Research Ethics Committee of Ngoerah General Hospital (Approval No: 2438/UN14.2.2.VII.14/LT/2024).

Conflict of Interest

The authors declare that they have no conflicts of interest or competing interests related to the content of this manuscript.

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