

EFFECT OF FERRITIN LEVELS ON THE OUTCOME OF DENGUE INFECTION IN CHILDREN

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Abstract

Background Appropriate supportive care and early diagnosis can lower the mortality risk in patients with severe dengue illness. To correctly identify patients most likely to benefit from suitable early therapies, it is essential to identify risk factors linked to severe types of dengue illness. A common feature of many disorders is hyperferritinemia, which is defined by a high degree of immunological activation, which includes hemophagocytic lymphohistiocytosis and macrophage activation syndrome, which in turn causes cytokine storms. Ferritin has been demonstrated in earlier research to be a useful marker in the distinction between dengue and other feverish illnesses. Therefore, the goal of the current investigation was to determine whether serum ferritin levels and dengue infection severity are correlated. **Methods** This descriptive cross-sectional study was conducted between October 2021 to September 2023, spanning two years, among children aged one to sixteen who were admitted to the paediatrics department of Saveetha Medical College and Hospital, Thandalam, exhibiting symptoms of fever, abdominal pain, vomiting, and/or decreased urine output. Clinical signs and symptoms, including positive NS1 antigen if they appear within 5 days of illness or IgM/IgG if they appear beyond 5 days, were used to diagnosis dengue infection. Measurements of serum ferritin were made on the first day of admission. Since every kid has a different day of sickness and admission, the serum ferritin level on the first day of admission was used as a proxy for the outcome. If a child's ferritin level was > 500 according to the HLH criteria, they were diagnosed with hyperferritinemia. **Results** There were 65 children in the study. There were 33 boys and 32 girls in the study group, which was a comparable distribution of males and females. 8.9 years was the average age. Of the study population, 53.8% tested positive for the NS1 antigen, 84.6% tested positive for dengue IgM, and 26.1% tested positive for dengue IgG. Of the participants in the research, 53.8% had hyperferritinemia. A statistically significant correlation was found between hyperferritinemia and positive dengue IgM test results. The amount of NS 1 antigen and dengue IgG did not show any statistical significance. Children that are stunted or underweight have elevated ferritin levels. A PICU admission was required for every child with elevated ferritin levels, a statistically significant finding. Hyperferritinemia subjects were statistically significantly ($p = 0.000$) more likely to experience shock, PICU hospitalisation, and inpatient days. The total WBC count (3872.4 ± 1481.11) and platelet count (0.605 ± 0.313) were significantly lower in children with hyperferritinemia. A statistically significant rise was observed in the levels of SGOT (181.77 ± 151.99) and SGPT (74.57 ± 74.79) in children diagnosed with hyperferritinemia. **Conclusion** One potential clinical sign of DENV infection is hyperferritinaemia. Ferritin may also be used as a marker for dengue infection severity in terms of hospital stay, shock, and fluid spacing. Elevated liver enzymes indicate more liver damage in children with hyperferritinemia.

Keywords: Dengue Infection, Hyperferritinemia, Ferritin Levels.

INTRODUCTION

Appropriate supportive care and early diagnosis can lower the mortality risk in patients with severe dengue illness. To correctly identify patients most likely to benefit from suitable early therapies, it is essential to identify risk factors linked to severe types of dengue illness. Acute-phase reactant ferritin is abundantly expressed by reticulo-endothelial system cells in response to inflammation and infection. A common feature of many disorders is hyperferritinemia, which is defined by a high degree of immunological activation, which includes hemophagocytic lymphohistiocytosis and macrophage activation syndrome, which in turn causes cytokine storms. In the absence of NS1 positivity, ferritin may be a useful marker for distinguishing dengue from other febrile illnesses, according to earlier research.^[1] Numerous investigations have demonstrated that infants with severe dengue exhibit noticeably elevated blood ferritin levels. Early in the course of a viral infection, an acute phase reactant ferritin may be slightly elevated; however, an acute phase reactant of early infection cannot account for the noticeably elevated ferritin in severe instances during the defervescence stage of infection. Therefore, it appears that the severity of the disease is connected to the increase in ferritin levels seen in instances of dengue hemorrhagic fever.^[2]

Therefore, the goal of the current investigation was to determine whether serum ferritin levels and dengue infection severity are correlated.

METHODS

This descriptive cross-sectional study was conducted between October 2021 to September 2023, spanning two years, among children aged one to sixteen who were admitted to the paediatrics department of Saveetha Medical College and Hospital, Thandalam, exhibiting symptoms of fever, abdominal pain, vomiting, and/or decreased urine output. Clinical signs and symptoms, including positive NS1 antigen if they appear within 5 days of illness or IgM/IgG if they appear beyond 5 days, were used to diagnosis dengue infection. Measurements of serum ferritin were made on the first day of admission. Since every kid has a different day of sickness and admission, the serum ferritin level on the first day of admission was used as a proxy for the outcome. Children were considered to have hyperferritinemia if their ferritin level was > 500 according to the HLH criteria.^[3]

RESULTS

Table 1: Comparison of Ferritin Levels with NS1, Dengue IgM and Dengue IgG

| Serum Ferritin | | Normal (30) | Hyperferritinemia (35) | χ^2 | P-Value |
|----------------|----------|-------------|------------------------|----------|---------|
| NS 1 Ag | Positive | 16 | 19 | 0.006 | 0.939 |
| | Negative | 14 | 16 | | |
| IgM | Positive | 22 | 33 | 5.448 | 0.02 |
| | Negative | 8 | 2 | | |
| IgG | Positive | 6 | 11 | 1.092 | 0.298 |
| | Negative | 24 | 24 | | |

Of the participants in the research, 53.8% had hyperferritinemia. Forty-two percent of them had ferritin levels that were normal. The ferritin levels are shown in Table 1 alongside the test parameters. Hyperferritinemia was found to be statistically significantly correlated with dengue IgM test positivity when ferritin levels were

compared to the different test parameters. The amount of NS-1 antigen and dengue IgG did not show any statistical significance.

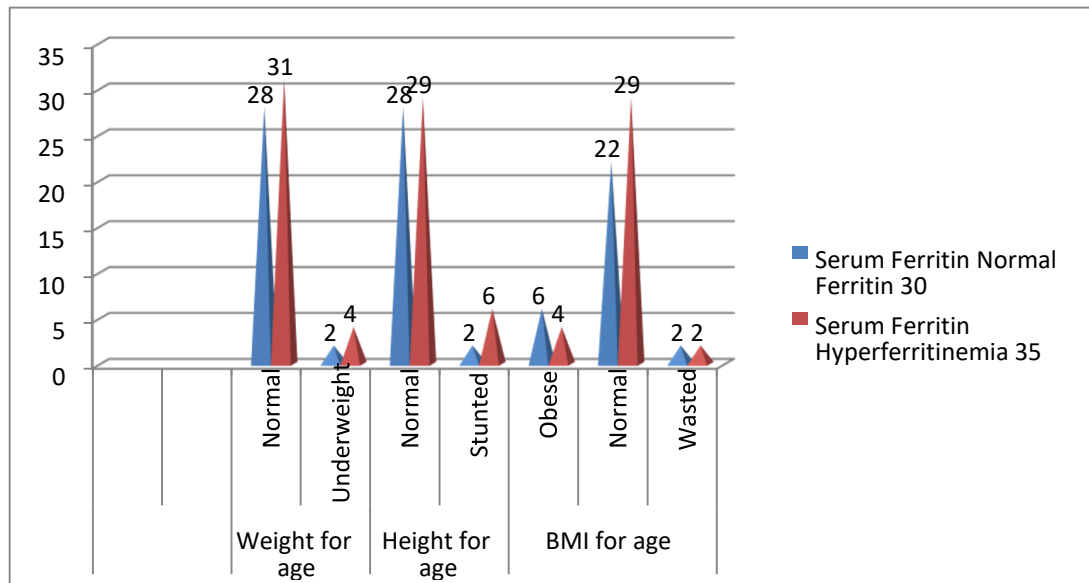


Figure 1: Comparison of Ferritin Levels with Anthropometry

Underweight and stunted children had elevated ferritin levels, as Figure 1 illustrates. This result, however, lacked statistical significance.

Table 2: Comparison of Days of Stay, Shock and Symptoms with Ferritin Levels

| Factors | | Serum Ferritin | | χ^2 | P-Value |
|--------------------|-------------|----------------------------|-------------------------------|----------|----------|
| | | Normal Ferritin (30) N (%) | Hyper Ferritinemia (35) N (%) | | |
| Days of Stay | 3- 5 days | 29 (96.7) | 02 (5.7) | 53.757 | 0.000*** |
| | 6-7 days | 0 | 21 (60) | | |
| | 8 – 10 days | 01 (3.3) | 12 (34.3) | | |
| PICU | NO | 30 (100) | 25 (71.4) | 10.130 | 0.001*** |
| | Yes | 0 | 10 (28.6) | | |
| Shock | No | 29 (96.7) | 07 (20) | 38.425 | 0.000*** |
| | Yes | 01 (3.3) | 28 (80) | | |
| Symptoms | | | | | |
| Abdominal Pain | No | 18 (60) | 12 (34.3) | 4.298 | 0.038** |
| | Yes | 12 (40) | 23 (65.7) | | |
| Vomiting | No | 17 (56.7) | 09 (25.7) | 6.448 | 0.011** |
| | Yes | 13 (43.3) | 26 (74.3) | | |
| Fluid Accumulation | No | 30 (100) | 28 (80) | 9.388 | 0.013** |
| | Yes | 0 | 07 (20) | | |
| Mucosal Bleeding | No | 30 (100) | 29 (82.9) | 5.666 | 0.017** |
| | Yes | 0 | 06 (17.1) | | |
| Lethargy | No | 24 (80) | 25 (71.4) | 0.640 | 0.424 |
| | Yes | 06 (20) | 10 (28.6) | | |
| Hepatomegaly | No | 19 (63.3) | 16 (45.7) | 2.018 | 0.155 |
| | Yes | 11 (36.7) | 19 (54.3) | | |

***p<0.01 - *p<0.05 (alpha Value) - statistically significant, ns- not significant, BMI - Body Mass Index, PICU – Pediatric Intensive Care Unit

The hospital stay, circulatory shock, and symptoms of children with normal ferritin and hyperferritinemia are compared in Table 2. Hyperferritinemia subjects were statistically significantly ($p = 0.000$) more likely to experience shock, PICU hospitalisation, and inpatient days. There was a significant increase in the incidence of abdominal pain, vomiting, fluid retention, and mucosal bleeding in those with hyperferritinemia. Children with hyperferritinemia had longer hospital stays, and this difference was statistically significant ($p = 0.000$). The statistical significance of the necessity for PICU hospitalisation was high for all the children with elevated ferritin levels. Positive correlations between serum ferritin levels and shock were observed. Children with elevated ferritin levels had higher rates of vomiting, fluid buildup, and mucosal bleeding; these differences were statistically significant ($p = 0.011$, $p = 0.013$, and $p = .017$, respectively). The following characteristics were not statistically linked to hyperferritinemia: weight for age, BMI, and clinical symptoms such as hepatomegaly and tiredness.

Table 3: Comparison of Demographic, Circumference, Blood Parameter, Renal and Liver Parameter with Ferritin Level

| Parameter | Serum Ferritin | | T-Value | P-Value |
|-----------------------------|--|---|---------|----------|
| | Normal Ferritin Mean \pm SD N =30 | Hyper Ferritinemia Mean \pm SD N =35 | | |
| Demographic Profile | | | | |
| Age | 9.20 \pm 4.15 | 8.77 \pm 3.35 | -0.460 | 0.653 |
| Circumference | | | | |
| Mid Upper Arm Circumference | 17.76 \pm 5.77 | 20.11 \pm 2.49 | -0.504 | 0.616 |
| Blood Parameter | | | | |
| Haemoglobin | 12.37 \pm 1.34 | 12.53 \pm 2.12 | -0.364 | 0.717 |
| Platelets | 1.409 \pm .656 | 0.605 \pm .313 | 6.444 | 0.000*** |
| Packed cell Volume | 37.32 \pm 4.24 | 38.57 \pm 4.66 | -1.12 | 0.267 |
| Totl Leucocyte count | 5256.51 \pm 2043. 20 | 3872.4 \pm 1481.11 | 3.157 | 0.002*** |
| Renal Parameter | | | | |
| Urea | 17.80 \pm 4.99 | 20.37 \pm 7.55 | -1.589 | 0.117 |
| Creatinine | .4700 \pm .134 | .485 \pm .121 | -0.495 | 0.622 |
| Liver Parameter | | | | |
| SGOT | 89.20 \pm 69.61 | 181.77 \pm 151.99 | -3.069 | 0.003*** |
| SGPT | 43.63 \pm 41.69 | 74.57 \pm 74.79 | -2.012 | 0.048* |
| ALP | 146.27 \pm 53.35 | 157.77 \pm 44.97 | -0.943 | 0.349 |

Values are expressed as Mean \pm SD; p value calculated using independent student – t test, * $p < 0.05$ - *** $p < 0.01$ - statistically significant, ns- not significant, SGOT – Serum Glutamic Oxalo Acetic Transaminase, SGPT- Serum Glutamic Pyruvic Transaminase, ALP –Alkaline Phosphatase

The comparison of laboratory data, anthropometry, and demographic profile with ferritin levels is shown in Table 3. It was highly noteworthy that children with elevated ferritin levels had lower platelet and total WBC counts. Children with hyperferritin showed statistically significant increases in SGOT and SGPT levels.

DISCUSSION

The current investigation discovered a strong correlation between severe dengue fever and a high blood ferritin level at the time of admission. Patients with dengue shock syndrome and dengue hemorrhagic fever had mean serum ferritin levels that were considerably greater than those with dengue fever. The official HLH guidelines

classified ferritin levels ≥ 500 mg/L as hyperferritinaemia.^[4] Of our participants, 834.26 ± 607.93 was the average ferritin value, and 35 out of 65 had hyperferritinemia. In dengue, hyperferritinaemia was closely linked to thrombocytopenia, elevated liver enzyme levels, and activation of the fibrinolytic and coagulation systems.^[5,6] The current study discovered that children infected with dengue who had hyperferritinemia had a statistically significant ($p = 0.000$) drop in platelets when compared to dengue-infected children with normal serum ferritin levels. The average platelet level in children infected with dengue fever and with normal ferritin levels was 1.409 ± 0.656 , whereas those with hyperferritinemia had platelets of 0.605 ± 0.313 lakhs/cu.mm. Thrombocytopenia, one of the main signs of DENV infection, is believed to result from platelets attaching to activated endothelium cells.^[7] The study also discovered that those with elevated ferritin levels had higher levels of liver enzymes, including SGOT, SGPT, and ALP. In our study, children with hyperferritinemia also had higher haemoglobin values. It is widely agreed upon that plasma leakage is present when there is a 20% rise in hematocrit over baseline. A significant precondition for the majority of dengue complications is plasma leakage. The pace of fluid infusion and the extent of plasma leakage are assessed by hematocrit (HCT) monitoring. Our research revealed a correlation between reduced platelets and elevated haematocrit in cases of hyperferritinemia.

In contrast to our study of 575.75, which looked at markers of dengue infection severity, a study by Julia et al. found that the median serum ferritin level was 209.4 $\mu\text{g/L}$.^[8] We discovered that the outcomes of our study and the one conducted by Nereida Valero et al. were similar. Children with severe dengue had a higher prevalence of hyperferritinemia. According to a study by Soundravally et al., ferritin is a biomarker that can be used to predict the severity of dengue. Similar to our work, she discovered in her research that serum ferritin levels in severe dengue were 1264.71 ± 492.59 .^[9]

Rashmi et al. discovered that leucocyte counts less than 4,000 cells/cu.mm and reduced platelet counts of less than 1,000,000 cu.mm are indicators of the severity of dengue infection.^[10] In children with severe dengue, we also observed that leucocyte and platelet counts were in the lower range. There was a statistically significant correlation between low platelet and leucocyte counts and hyperferritinemia. In our investigation, the platelet and leucocyte counts of children with hyperferritinemia were found to be 60,000 and 3800, respectively. Prior to the development of RT-PCR or the NS1 antigen assay, leukopenia was suggested as a diagnostic tool because of its historical association with dengue infections.^[11]

In terms of liver enzymes, all types of dengue infection were associated with elevations due to hepatic dysfunction; children with severe dengue had a statistically significant preference for higher SGOT than SGPT when compared to dengue fever. Hyperferritinemia was also connected with these elevated liver enzymes. In our study, children with severe dengue had an average SGOT of 181.77 ± 151.99 and an average SGPT of 74.57 ± 74.79 . This observation of hyperferritinemia and increased liver enzymes was consistent with the findings of Lian Huat Tan et al.'s investigation. He came to the conclusion that during and after the plasma leakage phase of dengue infection, children with severe dengue had high transaminases and significantly raised ferritin levels.^[12] In a retrospective investigation, Soumyabrata Roy Chaudhuri et al. investigated the potential utility of serum ferritin levels as a surrogate measure for DENV infection in contrast to other febrile illnesses with either an infectious or

inflammatory aetiology. In their investigation, the ferritin, SGOT, and SGPT levels in dengue-affected children were 200.5, 130.5, and 2745, respectively. This rise in serum ferritin and liver enzymes in dengue-affected youngsters is comparable to what we found in our study.^[13] Children with elevated serum ferritin levels have more liver damage, according to X. B. Zhang et al. investigation on the relationship between liver enzymes and serum ferritin levels in dengue-affected children.^[14] In their investigation, binary logistic regression analysis revealed that hyperferritinemia (SF \geq 500 ng/ml) was a risk factor for liver damage and dengue fever (OR = 8.120, P < 0.001). The ROC curve study also showed that at a serum ferritin cut-off value of 1506 ng/ml, the sensitivity was 74.8% and the specificity was 83.3%. The area under the curve for judging the combined liver damage caused by dengue fever was 0.846 (95% CI: 0.785–0.908). They come to the conclusion that hyperferritinemia is a risk factor for dengue fever paired with liver damage and that there is some association between the serum ferritin level and the severity of liver damage in patients with dengue fever who are in the acute stage of the illness.

In Bangkok, Thailand, Wathanee Chaiyaratana et al.^[15] carried out research to assess ferritin levels and their predictive value for DHF (Dengue Hemorrhagic Fever). With an average age of 11, they enlisted 177 kids between the ages of 4 and 16. 44 of these were kids with DF, and 133 had DHF. Serum ferritin levels were tracked from the time of hospitalisation until 2-4 weeks following discharge. To determine the sensitivity and specificity for DHF, they employed a threshold level of 1200 ng/ml for serum ferritin. The findings showed that the specificities were 42.4, 39.0, and 36.4%, respectively, while the sensitivities of blood ferritin levels on days 5, 6, and 7 of sickness were 81.5, 84.4, and 89.9%, respectively. According to the study's findings, a high serum ferritin level of 1,200 ng/ml or higher may be a sign of dengue hemorrhagic fever.

Similar to our investigation, a study by Cornelia A. M. Van De Weg et al. found a substantial correlation between hyperferritinaemia and thrombocytopenia, increased liver enzymes, and coagulation abnormalities.^[16]

Another predictive factor for determining the severity of dengue is abdominal pain. It might result from a decrease in blood flow to the visceral organs during the shock or pre-shock phase, which would cause tissue hypoxia. Abdominal pain can also result from hepatomegaly, intestinal haemorrhage, or both.^[17] In our study, hyperferritinemia was present in 66% of the participants who reported stomach pain. Other cautionary indicators, such as hepatomegaly, vomiting, fluid retention, mucosal bleeding, and fatigue, were more common in the hyperferritinemia group than in the participants with normal ferritin levels. All of these warning indicators were significantly more prevalent in people with elevated ferritin levels, even if these results were not statistically significant.

CONCLUSION

One potential clinical sign of DENV infection is hyperferritinaemia. Ferritin may also be used as a marker for dengue infection severity in terms of hospital stay, shock, and fluid spacing. Elevated liver enzymes indicate more liver damage in children with hyperferritinemia.

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