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FERRITIN AS A PROGNOSTIC MARKER OF DISEASE SEVERITY IN DENGUE FEVER

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Abstract

Background: Every year, as many as 400 million individuals worldwide become infected with severe dengue, and 22,000 die as a result. Dengue fever is a leading cause of acute febrile disease worldwide, particularly in the tropics and subtropics. Reticulo-endothelial cells heavily generate ferritin, an acute-phase reactant, in response to infection and inflammation. Serum ferritin levels are generally elevated after dengue virus infection.

Objective: To detect Ferritin as a predictive marker of illness severity in Dengue Fever.

Methodology: A cross-sectional observational research was conducted in the Department of medicine, Bolan medical college/ Bolan medical complex hospital Quetta. The study duration was one year from March 2023 to March 2024. Our study comprised a total of 200 patients. Our study comprised patients who were diagnosed with Dengue fever based on their clinical examination, history, and positive "nonstructural protein 1 (NS 1) antigen" or "Dengue IgM antibodies". Upon admission, all patients had their serum ferritin levels tested using ELISA. Individuals were placed into two groups based on their serum ferritin levels. All data were analyzed using the SPSS 24 version.

Results: Out of two hundred individuals, 130 (65%) were males and 70 (35%) were females. The average age of patients was 31.12 (±8.73) years. The average hospital stay lasted 4 (±1.22) days. 150 (75%) patients had serum ferritin levels over 100 µg/dl, whereas 50 (25%) had levels below 100 µg/dl. Out of 50 with normal levels of ferritin, only 4 (8%) acquired severe dengue, whereas 120 (60%) of 150 developed severe dengue (p=0.0001).

Conclusion: Elevated levels of ferritin in the blood are substantially related with severe dengue. In individuals having severe type of dengue, the mean of ferritin levels are higher than those with dengue fever. The level of ferritin in the blood upon first examination may be a biomarker for predicting the degree of illness in dengue.

Key words: Ferritin; Prognostic marker; Dengue Fever; DSS

Introduction

Dengue fever (DF) is a serious health issue, with fifty million cases reported year globally. Records showed that dengue founds over 100 nations and is spreading to previously untouched places [1]. The dengue virus causes arboviral fever. The cause of dengue are five Dengue virus serotypes: “DENV1”, “DENV2”, “DENV3”, “DENV4”, and “DENV-5”, and is transferred to humans by a vector an Aedes mosquito. [2] [3]. Dengue by any serotype normally causes infection which is asymptomatic or moderate non-specific febrile illness, but in certain people, severe disease occurs, defined by a “transitory capillary leakage syndrome” (dengue hemorrhagic fever DHF).

Laboratory identification of dengue fever is critical for providing appropriate therapy to patients and preventing possible complications such as “dengue hemorrhagic fever” (DHF) and “dengue shock syndrome” (DSS), which are both classified by WHO as severe dengue [4]. The host's immunity plays a significant part in dengue’s pathogenesis [5]. The specific mechanism of dengue's many symptoms is not yet fully known. The most widely recognized idea is that viral strains from subsequent infections cause enhanced memory T-cell production, and antibody production which leads in a cytokine boost [6]. Other possibilities examined include the change to a Th-2 response in severe dengue from a Th-1 response in moderate dengue [7]. These eventually cause hemorrhage and shocks due to injury to the endothelium, platelets, and different organs, resulting in coagulopathy and vasculopathy [8].

This fickle clinical history, as well as the necessity to identify DF from other causes of fever, are critical for making an immediate and accurate diagnosis of acute infection with the dengue virus. Among arboviral infections Dengue fever remains the leading etiological agent of epidemic outbreaks [9]. The fatality of dengue is usually recorded as 1%, although it can reach 3-5% in some rural areas of India and Pakistan [10]. Damage to endothelial cells and capillary leakage caused by enhanced capillary permeability can account for dengue fever's clinical characteristics [5]. Alog with other established laboratory indicators of dengue, the levels of serum ferritin have been also linked with the severity of dengue illness.

Hyperferritinaemia occurs when the levels of ferritin exceed 500 µg/L. Ferritin is a reactant in the acute phase that reticulo-endothelial cells generate in large quantities in response to inflammation and infection [11]. Ferritin binds to iron, reducing the amount available in the circulation. Because many harmful bacteria require iron for growth, this process benefits the host. Furthermore, iron deprivation advances the immune function of neutrophils, lymphocytes, and macrophages. Hyperferritinaemia is a characteristic of disorders that involve substantial immunological activation, such as “macrophage activation syndrome (MAS)” and “hemophagocytic lymphohistiocytosis (HLH)” [11]. HLH can be hereditary or caused by an external stimulation such as cancer or an infection with a virus, including dengue. In HLH patients, CD8+ T lymphocytes and Natural Killer cells have poor cytotoxic activity, resulting in diminished elimination of infectious and APCs “antigen-presenting cells” from the blood. This may cause an excessive immunological response, including the expansion of tissue macrophages, T-cells and dendritic cells, which contributes to a cytokine cyclone. [11]

Methodology

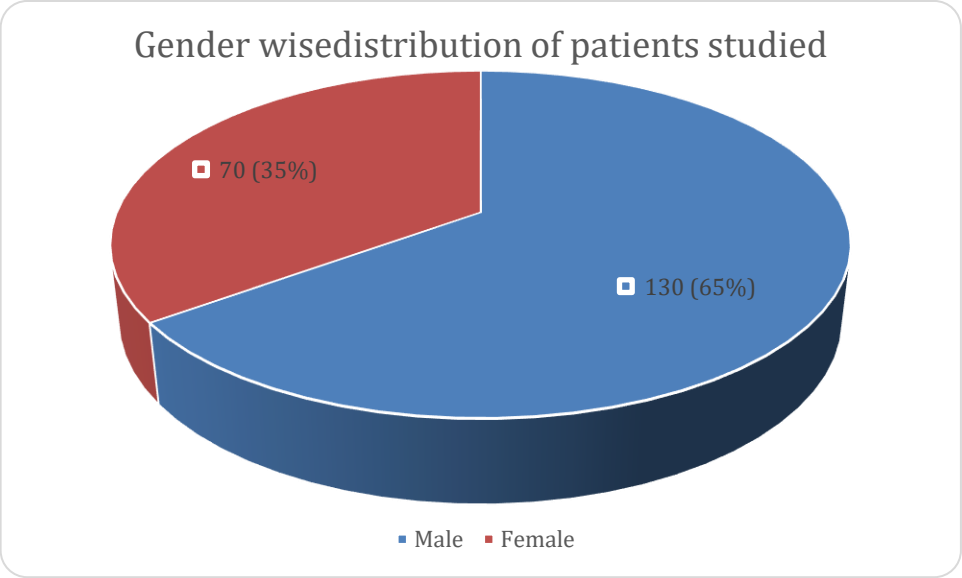
A cross-sectional observational research was conducted in the Department of medicine, Bolan medical college/ Bolan medical complex hospital Quetta. The study duration was one year from March 2023 to March 2024. Our study comprised a total of 200 patients. Patients hospitalized were tested for CBC, ferritin NS1 protein, and IgM.

Inclusion Criteria: This study involved individuals already diagnosed with Dengue fever on the basis of their history, clinical examination, and the presence of a “positive non-structural protein 1 (NS1) antigen” or Dengue “IgM” antibodies. On the day of admission, all patients had their serum ferritin levels tested using ELISA.

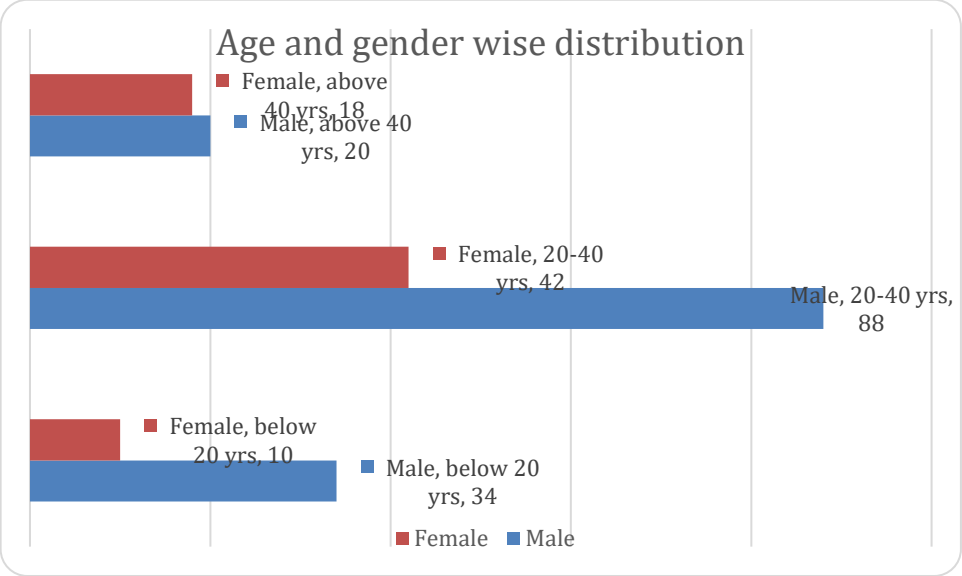
Exclusion criteria those with microcytic anaemia who presented with DHF or DSS were excluded, as were those with acute febrile disease other than dengue, and pregnant women.

Statistical Analysis The data were put into a Microsoft Excel 2010 spreadsheet and analyzed using SPSS 24. Tables were created for the variables. The study's variables were studied using the Pearson chi-square test. Results for continuous measures are reported as mean ± SD. In this study, 'p' values < 0.05 were deemed significant. Ethical Committee granted the ethical approval. Procedure: Patients were placed into two groups based on ferritin levels. . Patients with values more than 100 µg/dl had elevated levels of serum ferritin. Group A comprised patients with ferritin levels of 100 µg/dl, whereas Group B included individuals with ferritin levels greater than 100 µg/dl.
Patients with warning indications of ,decreased platelet count, mucosal bleeding, increased haematocrit, buildup of fluid, severe plasma leakage, abdominal discomfort, excessive bleeding, and organ failure were classified as having severe dengue. The study's end goal was determined by whether patients experienced severe dengue while hospitalized or were released from the hospital without incident. By using ELISA, dengue IgG, IgM, and NS1 were measured. On the day of admission, the pathology department assessed the serum ferritin level of every patient using an ELISA.

Results
200 individuals who were hospitalized with a suspicion of dengue fever participated in this research. The findings of the study are displayed in the graph and tables that follow. Three quarters of the 200 patients were female, or 70 individuals, and 65% of the patients, or 130 patients, were male.



Of the 200 patients, the majority were between the ages of 20 and 40, with the next age groups being under 20 and over 40, respectively. 16% (128) of the patients were between the ages of 20 and 40, while 19% (38) were above 40. The mean age of the individuals in this research was 31.12 ± 8.73 years. While the hospital stay lasted an average of 4 ± 1.22 days. The fever lasted for an average of 5.5 ± 1.91 days.



Thirty male patients and twenty female individuals had serum ferritin levels <100 µg/dl, whereas fifty male patients and one female patient had serum ferritin levels >100 µg/dl.

Table 1: Serum ferritin levels distribution between genders

Serum ferritin	Male	Female	Total
< 100 µg/dl	**30**	**20**	**50**
> 100 µg/dl	**100**	**50**	**150**
Total	**130**	**70**	**200**

Only 4 patients out of 50 with serum ferritin level less than 100 µg/dl showed severe dengue while on the other hand 120 out of 150 with serum ferritin level more than 100 µg/dl showed severity in dengue illness.

Table 2: Relationship between ferritin and severity of dengue

Serum Ferritin	Severe Dengue NO	Severe Dengue Yes	P value
Serum Ferritin level **<100 µg/dl** (N=50)	**46**	**4**	**0.0001**
Serum Ferritin level **>100 µg/dl** (N=150)	**30**	**120**	**0.001**

To study the variables and the relationship between the degree of severity of dengue and serum ferritin the chi square test was employed by using SPSS 24. According to this table, patients having severe dengue showed higher blood ferritin levels at the time of admission than those with less severe cases. A p value < 0.05 showed the results were statically significant. . Out of fifty patients in group A, 4 had severe dengue with ferritin levels less than 100 µg/dl. In contrast, 120 patients in group B had severe dengue with ferritin levels greater than 100 µg/dl.

Discussion

Our study showed that of the 200 patients in my research, 65% were men (the majority) and 35% were women. The average length of hospitalization was (4 ± 1.12) days, and 4 of the 50 patients experienced severity in dengue with less than 100 µg/dl serum ferritin levels. Similar study that Males comprised 59.19% of the patient population in a research by Selvamuthukumaran S. A 5±2 day

hospital stay was the average. Twelve patients out of thirty with ferritin levels in the range of 200 and 300 ng/dl and thirty out of forty-nine individuals with ferritin levels in the range of 300 and 400 ng/dl and forty-six out of sixty-two individuals with ferritin levels ranged from 400 and 500 ng/dl and six individuals with ferritin levels between 500 and 600 ng/dl developed severe dengue [12].

Another study report that mean age of the patients in a research by Nadeem M et al. was reported as (30.7 ± 13.8) years. The fever lasted for an average of 5.6 ± 1.3 days. The hospital stay lasted an average of 3.7 ± 1.02 days. Only 30% of patients had serum ferritin levels < 100 µg/dl, whereas 70% of patients had levels > 100 µg/dl. Patients with severe dengue fever had mean ferritin levels of 317.54 ± 109.52, which was significantly higher than the mean ferritin levels of 168.69 ± 130.7 in patients with simple dengue fever. [13] The mean age of the individuals in our research was 31.5 ± 11.2 years. The fever lasted for an average of 5.3 ± 1.81 days.

The average serum ferritin level was significantly higher in patients with severe dengue (861.28 ± 183.17) than in patients with non-severe dengue (400 ± 151.7). Serum ferritin values above 600 ng/dl in 60% of patients, whereas 40% of patients had values below 600 ng/dl. Ahmed A et al.'s study revealed that the average length of hospitalization was 2.74 ± 1.42 days, while the average duration of fever was 5.49 ± 2.65 days. [14] A research carried by Soundravally et al., found that high ferritin levels had almost 77% sensitivity and 83% specificity for guessing dengue severity on the day of admission [15]. In our investigation, a significant correlation was discovered between the development of severe dengue during a hospital stay and elevated blood ferritin levels on the day when they were examined. The same was demonstrated by many foreign investigations. Research from Aruba and Brazil revealed a considerable correlation between higher ferritin and the severity of dengue virus infection. [16]

Conclusion

Serum ferritin levels that are elevated have a substantial correlation with severe dengue. The individuals having severe dengue also exhibited greater mean levels of ferritin than the individuals with mildS DF. Serum ferritin levels on the day of hospitalization can be a useful biomarker for timely assessment of the severity of the sickness when a dengue virus infection is present.

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