

# COMPARISON BETWEEN THE LEVELS OF FERRITIN SERUM ON PATIENTS WITH FEVER OF UNKNOWN ORIGIN TO DIFFERENTIATE INFECTIOUS AND NONINFECTIOUS DISEASES

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## Introduction

Fever of Unknown Origin (FUO) is classified as fever in excess 38,3°C (101°F) lasting for more than 3 weeks, where the cause could not be revealed despite multiple diagnostic tests during three visitations to the outpatient department or during 3 days of hospitalization. During fever, the body releases inflammatory cytokines which also increases the synthesis of serum ferritin. The purpose of this research is to determine whether serum ferritin levels could be used to differentiate between FUO caused by infectious and noninfectious diseases and to find an optimal cutoff value to predict that.

## Materials and Methods

FUO patients were hospitalized at Hosana Lippo Cikarang Hospital from 1 December 2018-30 November 2019. The method of this research is an observational analytic with a cross sectional approach. The subject of this research are 30 people from each group. The data measured is serum ferritin. The data is analyzed using the Mann Whitney statistical test with  $\alpha=0.05$ .

## Results

The average of serum ferritin levels in FUO infectious diseases (294±54 ng/mL) was lower than those in noninfectious diseases (762±355 ng/mL) with  $p=0.000$ . The optimal cutoff value of serum ferritin levels to differentiate FUO caused by infectious or noninfectious diseases was established 396.5 ng/mL.

Group	Mean (ng/mL) ± SD <sup>^</sup>	Median (ng/mL) (minimum-maximum)	p-value*
Infectious disease	294±54	290(189-412)	0.000
Non-infectious disease	762±355	638(399-1818)	

<sup>^</sup> SD = Standard Deviation

\*Statistical analysis was performed using the Mann-Whitney test

Table 1 The mean (standard deviation and range of the mean) and median values (interquartile range) of the serum ferritin levels for infectious and non-infectious diseases groups

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## Discussion

Serum ferritin levels in FUO with infectious and non infectious diseases were higher than reference value of ferritin (15-200 ng/mL). This increase was due to inflammation in FUO patients. Fever is one of the most common symptoms that indicate a disease, including in FUO. The body produces inflammatory cytokines, especially interleukin-1 (IL-1), interleukin-6 (IL-6), Tumor Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) and interferon (IFN) that cause fever responses. Interleukin-6 is one of the cytokine directly regulates hepcidin through induction and subsequent promoter binding of signal transducer and activator of transcription 3 (STAT3). Hepcidin causes the degradation of ferroportin thereby reducing iron transport from cells that causes iron retention in cells so that iron storage is increased as reflected by an increase in serum ferritin. Inflammatory cytokines such as IL-1, IL-6, TNF- $\alpha$  and IFN will increase serum ferritin levels by modulating the transcription and translation pathways of the ferritin gene. The occurrence of cell damage can cause cell leakage thereby increasing serum ferritin levels.

Serum ferritin levels can also be used to differentiate between FUO individuals with non-infectious diseases and with infectious diseases. Microorganisms need iron for the replication process, therefore intracellular and extracellular iron will be reduced so that serum ferritin levels in infectious diseases will be lower than in non-infectious diseases.

## Conclusion

Ferritin serum could be used to differentiate FUO caused by infectious or noninfectious diseases with the cutoff value of 396.5 ng/mL.

### Key words:

Fever of Unknown Origin, ferritin serum, infectious/noninfectious diseases

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