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Diagnostic use of serum ferritin levels to differentiate infectious and noninfectious diseases in patients with fever of unknown origin

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Abstract.
INTRODUCTION: In this study, we determined whether serum ferritin levels could be used to differentiate between fever of unknown origin (FUO) caused by infectious and noninfectious diseases.
METHODS: FUO patients were hospitalized at Chonnam National University Hospital between January, 2005 and December, 2011. According to the final diagnoses, five causes were identified, including infectious diseases, hematologic diseases, noninfectious inflammatory diseases, miscellaneous and undiagnosed.
RESULTS: Of the 77 patients, 11 were caused by infectious diseases, 13 by hematologic diseases, 20 by noninfectious inflammatory diseases, 8 by miscellaneous diseases, and 25 were undiagnosed. The median serum ferritin levels in infectious diseases was lower than those in hematologic diseases and (median (interquartile range) of 282.4 (149.0–951.8) ng/mL for the infectious disease group, 1818.2 (485.4–4789.5) ng/mL for the hematologic disease group, and 563.7 (399.6–1927.2) ng/mL for the noninfectious inflammatory disease group, $p = 0.048$, Kruskal–Wallis test). By comparison using the Mann–Whitney test, statistically significant differences were found only between the infectious disease and hematologic disease groups ($p = 0.049$) and between the infectious disease and groups ($p = 0.04$).
CONCLUSION: An optimal cutoff value of serum ferritin levels to predict FUO caused by a noninfectious disease (hematologic diseases, noninfectious inflammatory diseases) was established as 561 ng/mL.

Keywords: Fever of unknown origin, ferritin

1. Introduction

In 1961, Petersdorf and Beeson defined a fever of unknown origin (FUO) as a case where a fever in excess of 38.3°C continued for more than 3 weeks, and its cause could not be identified by tests during hospitalization for more than 1 week [1]. As diagnostic techniques such as imaging technology and clinical tests have been developed and outpatient access to diagnostic tests have improved, Durack and Street in 1991 defined the FUO as a shortened period where the cause could not be revealed despite diagnostic tests during three visits to the outpatient department or during 3 days of hospitalization [2]. While the causes of FUO are diverse, they could be divided into four principal groups: neoplasms, infections, non-infectious inflammatory diseases (NIID, including rheumatic diseases and vasculitic diseases), and other diseases [1,3,4]. Despite the development of various diagnostic techniques, 34–51% of FUO patients remain undiagnosed [3,4].

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Physical examination and serologic tests have been used to narrow down the range of diseases and differentially diagnose or exclude possible causes. Serum ferritin was discovered by the French scientist Laufberger in 1937 and was first measured in serum using a radioimmunoassay method [5]. Although it is generally used as an index of the extent of iron storage in the body, it is also used as an acute phase reactant in response to inflammation [6]. When serum ferritin is enhanced (excluding transfusion and hemochromatosis), systemic lupus erythematosus, hematologic malignancy, liver diseases, hemophagocytic syndrome, and opportunistic infection by human immunodeficiency virus infection must be considered [7–9].

While some investigators suggested that serum ferritin may have a diagnostic value for FUO, clinical evidence is lacking. Also, Cunha et al. asserted that serum ferritin levels should be used in conjunction with medical history, physical examination, and other serological tests to exclude infectious diseases since the likelihood of infectious disease is low when early serum ferritin levels are elevated ($\geqslant$ 500 ng/mL) [10]. However, statistically significant data supporting this assertion is lacking. In another study, it was reported that low ferritin concentration ($<$ 500 ng/mL), eosinopenia ($\leqslant$ 40/mm^3) and high C-reactive protein (CRP $>$ 6 mg/dL) were associated with infectious diseases. Satisfying two of these three factors is predictive of FUO caused by an infectious disease [11]. However, since data for this study were collected over a span of 15 years, they may not have reflected changes in the causes of FUO or the trend in diagnostic methods. Also, it was limited by the fact that the majority of infectious diseases was previously caused by infective endocarditis, and hence generalized study results could not be applied to other infectious diseases, including tuberculosis, which has recently emerged as a major cause of FUO. Thus, we evaluated the validity of serum ferritin concentration for determination of the cause of FUO. We also propose an optimal value for differentiation of infectious and noninfectious diseases.

2. Subjects and methods

2.1. Subjects

Subjects included patients diagnosed with classical FUO, older than 15 years of age, who were hospitalized with fever at Chonnam National University Hospital from January 1, 2005, through December 31, 2011. Diagnostic criteria for classical FUO followed the suggestion of Durack et al. [2]. Patients included in this study had a fever in excess of 38.3°C, lasting for at least three weeks, of which no causes were identified after three visits to the outpatient care or three days after hospitalization. Subjects were excluded from this study if they had FUO related to neutropenia, acquired immunodeficiency syndrome, or nosocomial infection. Data on age, gender, fever duration before hospitalization, hospitalization period, history, early physical examination, serological test results, diagnostic method of confirming the final diagnosis, and final diagnosis were collected by a retrospective review of medical records.

2.2. Methods

For serological tests of patients with FUO, serum ferritin and erythrocyte sedimentation rates (ESR) were measured within 7 days of hospitalization, and white blood cell (WBC) count and C-reactive protein (CRP) were measured within 24 h of hospitalization. ARCHITECT T2000 SR equipment and the ARCHITECT ferritin reagent kit by Abbott was used to measure serum ferritin levels. The test method had a measurement limit of 0–2000 ng/mL (0–40000 ng/mL when diluted), with an analytical sensitivity of less than 1 ng/mL.

For infectious diseases, at least two specialists were consulted for diagnosis, while a physician specializing in hematology was consulted for diagnosis of hematologic diseases and a rheumatism specialist was consulted for NIID. For hemophagocytic syndrome, diagnosis followed the HLH-2004 guidelines [12], and diagnosis of adult-onset Still's disease followed the Yamaguchi criteria [13]. Patients confirmed as FUO were classified according to their final diagnoses into a total of five groups, including infectious diseases, hematologic diseases, NIID groups, a group diagnosed as diseases other than the former three diseases, and a group without final diagnoses (including death, transfer to another hospital and discharge against medical advice). Then, the correlations of patient clinical characteristics with serological tests and final diagnoses were analyzed.

2.3. Statistics

To evaluate the validity of serum ferritin levels to predict infectious or noninfectious diseases, AUROCs (areas under the ROC curve) were obtained using ROC(receiver operation characteristic) curves and were used as an index for diagnostic validity. Youden's in-

Table 1
Patient demographic characteristics of disease groups (means ± SD*)

	Infectious diseases ($n = 11$, 14.3%)	Hematologic diseases ($n = 13$, 16.9%)	Noninfectious inflammatory diseases ($n = 20$, 26%)	Miscellaneous ($n = 8$, 10.4%)	No diagnosis ($n = 25$, 32.5%)	p-value
Age	40 (24–65)	51 (45–56)	37 (18–55)	68 (52–81)	56 (43–70)	0.09
Male: female	7: 4	6: 7	12: 8	4: 4	14: 11	0.91
Duration of fever before admission, day	15 (7–28)	15 (9–34)	20 (19–30)	25 (14–30)	21 (14–30)	0.31
Duration of hospitalization, day	14 (7–23)	12 (7–19)	10 (6–16)	15 (11–21)	15 (10–19)	0.19
Cardiac murmur	0	0	1 (5%)	0	1 (4%)	0.83
Skin rash	1 (9%)	2 (15%)	4 (20%)	1 (13%)	5 (20%)	0.92
Arthralgia	2 (18%)	2 (15%)	4 (20%)	1 (13%)	3 (12%)	0.96
Myalgia	2 (18%)	5 (39%)	7 (35%)	0	9 (36%)	0.58
Hepatosplenomegaly	1 (9%)	3 (23%)	5 (25%)	0	5 (20%)	0.83
Lymphadenopathy	2 (18%)	2 (15%)	6 (30%)	2 (25%)	2 (8%)	0.41

Median (interquartile range); *SD = standard deviation.

Table 2
Cause of fever in FUO patients

Cause of fever	n (%)
Infectious diseases	11 (14.3)
Bacterial	
Tuberculosis	5 (6.5)
Typhoid fever	2 (2.6)
Viral	
EBV* infection	2 (2.6)
HIV† infection	1 (1.3)
Parasitic	1 (1.3)
Hematologic diseases	13 (16.9)
Hodgkin, non-Hodgkin's lymphoma	6 (7.8)
Hemophagocytic syndrome	4 (5.2)
Leukemia	2 (2.6)
Hypereosinophilic syndrome	1 (1.3)
Noninfectious inflammatory diseases	20 (26.0)
Connective tissue disease	
Kikuchi Fujimoto disease	6 (7.8)
Adult-onset Still's disease	4 (5.2)
Anti-phospholipid syndrome	3 (3.9)
Rheumatoid arthritis	2 (2.6)
Systemic lupus erythematosus	1 (1.3)
Sweet's syndrome	1 (1.3)
Rosai–Dorfman syndrome	1 (1.3)
Vasculitic syndrome	
Wegener's granulomatosis	1 (1.3)
Behçet's disease	1 (1.3)
Miscellaneous	8 (10.4)
Subacute thyroiditis	2 (2.6)
Pulmonary thromboembolism	2 (2.6)
Drug fever	2 (2.6)
Right ventricular thrombi	1 (1.3)
Gastric malignancy (sarcomatoid carcinoma)	1 (1.3)
No diagnosis	25 (32.5)

*EBV = Epstein–Barr virus; †HIV = human immunodeficiency virus.

dex J (J = sensitivity + specificity − 1) was used for selecting the optimal cutoff value of infectious disease, and positive and negative predictive values were calculated using these cutoff values. Results were considered statistically significant when p values were less than 0.05, and statistical comparisons were made using SPSS, version 18.0 (SPSS Inc., Chicago, Illinois). Statistical significance of non-continuous variables was verified by conducting cross-tabulation while that of continuous variables was performed using the Kruskal–Wallis test. When results of the Kruskal-Wallis test were statistically significant, the groups were reanalyzed using the Mann–Whitney test.

3. Results

3.1. Age, gender distribution and clinical signs

Seventy-seven patients with FUO were included in the study, consisting of 43 males and 34 females, with the median age of all patients being 51 years. Age distribution and gender per disease group are as shown in Table 1. Although there was no statistically significant difference among the five groups, the mean age of those in the undiagnosed group was greater ($p = 0.03$) compared with the diagnosed group [median (interquartile range), 50 years (32–61)] and undiagnosed group (56 years (43–70). Fever periods prior to hospitalization and clinical signs showed no significant differences among the disease groups (Table 1).

3.2. Disease group distribution

Eleven patients (14.3%) had FUO caused by infectious diseases, while 13 patients had FUO caused by hematologic disease (16.9%) and 20 patients by NIID (26.0%). A total of 8 patients had FUO caused by other diseases (10.4%), while no causes were found in

Table 3
Laboratory findings [median (IQR)], (Kruskal–Wallis test)

	Infectious diseases ($n = 11$)	Hematologic diseases ($n = 13$)	Noninfectious inflammatory diseases ($n = 20$)	p-value*
ESR (mm/hr)	60 (24–71)	60.5 (32.3–90.8)	84.5 (44–102.8)	0.28
CRP (mg/dL)	7.6 (2.8–15.0)	8.0 (3.3–19.3)	11.1 (3.2–17.7)	0.89
Ferritin (ng/mL)	282.4 (149.0–951.8)	1818.2 (485.4–4789.5)	563.7 (399.6–1927.2)	0.048†
Hemoglobin (g/dL)	9.5 (9.4–10.1)	9.6 (9.4–9.8)	9.5 (9.4–10.7)	0.58
WBC count ($\times 10^3$/mm^3)	11.5 (10.3–14.3)	11.1 (9.1–13.3)	11.7 (9.2–13.2)	0.76
Granulocyte count ($\times 10^3$/mm^3)	7.7 (5.4–15.0)	6.9 (3.55–16.15)	7.45 (3.78–11.48)	0.78
Lymphocyte count ($\times 10^3$/mm^3)	5.12 (4.0–11.82)	4.5 (1.67–12.93)	5.8 (2.01–8.93)	0.80
Monocyte count ($\times 10^3$/mm^3)	1.5 (0.92–1.81)	1.33 (0.7–1.88)	1.27 (0.81–1.56)	0.59
Eosinophil count ($\times 10^3$/mm^3)	0.6 (0.31–1.1)	0.62 (0.32–1.22)	0.49 (0.2–0.77)	0.71
Platelet count ($\times 10^3$/mm^3)	0.02 (0.0–0.67)	0.02 (0.0–0.55)	0.02 (0.0–0.1)	0.12

*Statistical analysis was performed using the Kruskal–Wallis test; †Statistically significant differences were found between infectious diseases and hematologic diseases ($p = 0.049$), as well as infectious diseases and non-infectious inflammatory diseases ($p = 0.04$) using the Mann–Whitney test. However, there was no significant difference between hematologic diseases and NIID ($p = 0.25$).

Table 4
Multivariate regression analysis for distinguishing between infectious and noninfectious disease

	Parameter estimate	Standard error	p-value	OR*	95% CI†
Ferritin ($<$ 500 ng/mL)	1.72	0.92	0.06	5.57	0.93–33.43
CRP ($>$ 6.0 mg/dL)	0.96	0.99	0.33	2.62	0.38–18.13
Eosinopenia ($<$ 40/mm^3)	0.09	0.78	0.91	1.10	0.24–5.02

*OR = odd ratio; †CI = confidence interval.

25 patients (32.5%). Common diseases included lymphoma (six patients, 7.8%), Kikuchi Fujimoto disease (six patients, 7.8%), tuberculosis (five patients, 6.5%), hemophagocytic syndrome (four patients, 5.2%), and adult onset Still's disease (four patients, 5.2%) (Table 2).

3.3. Methods used to obtain final diagnoses

Methods used to diagnose causes of FUO included biopsy (23 patients), clinical diagnosis (16 patients), rheumatologic serum tests (4 patients), imaging studies (3 patients-chest computed tomography for 2 patients, transthoracic echocardiography for 1 patient), and serum viral marker tests (3 patients).

3.4. Serologic test results for infectious disease and noninfectious disease groups

The ESR, CRP, WBC count, WBC fraction, and platelet count did not differ significantly among the three disease groups. Serum ferritin was measured in 73 of 77 subjects within 7 days of visiting the hospital (missing data were treated as list-wise deletions). Of these, 48 cases received a final diagnosis, and 25 cases were not diagnosed (Fig. 1). Serum ferritin showed statistically significant differences among the three groups, being 282.4 (149.0–951.8) ng/mL in the infectious disease group, 1818.2 (485.4–4789.5) ng/mL in the hematologic disease group, and 563.7 (399.6–1927.2) ng/mL in the NIID group ($p = 0.048$) (Table 3). Based on a Mann–Whitney test, serum ferritin levels differed significantly ($p = 0.049$, $p = 0.04$) between the infectious disease and hematologic disease

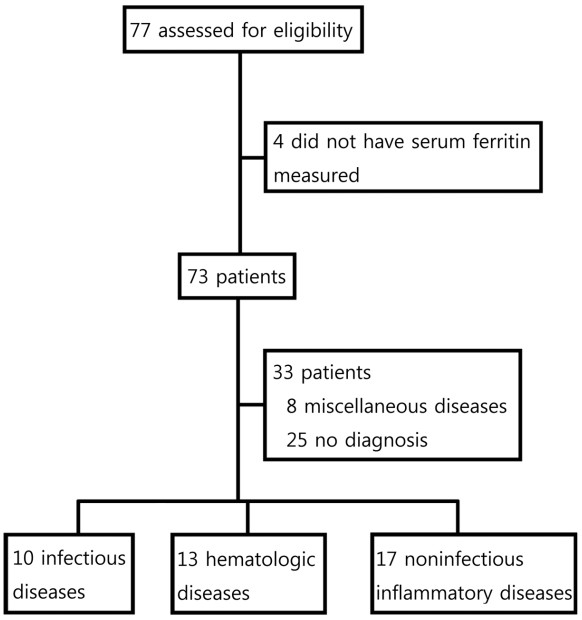


Fig. 1. Flow sheet of ferritin analyzed groups.

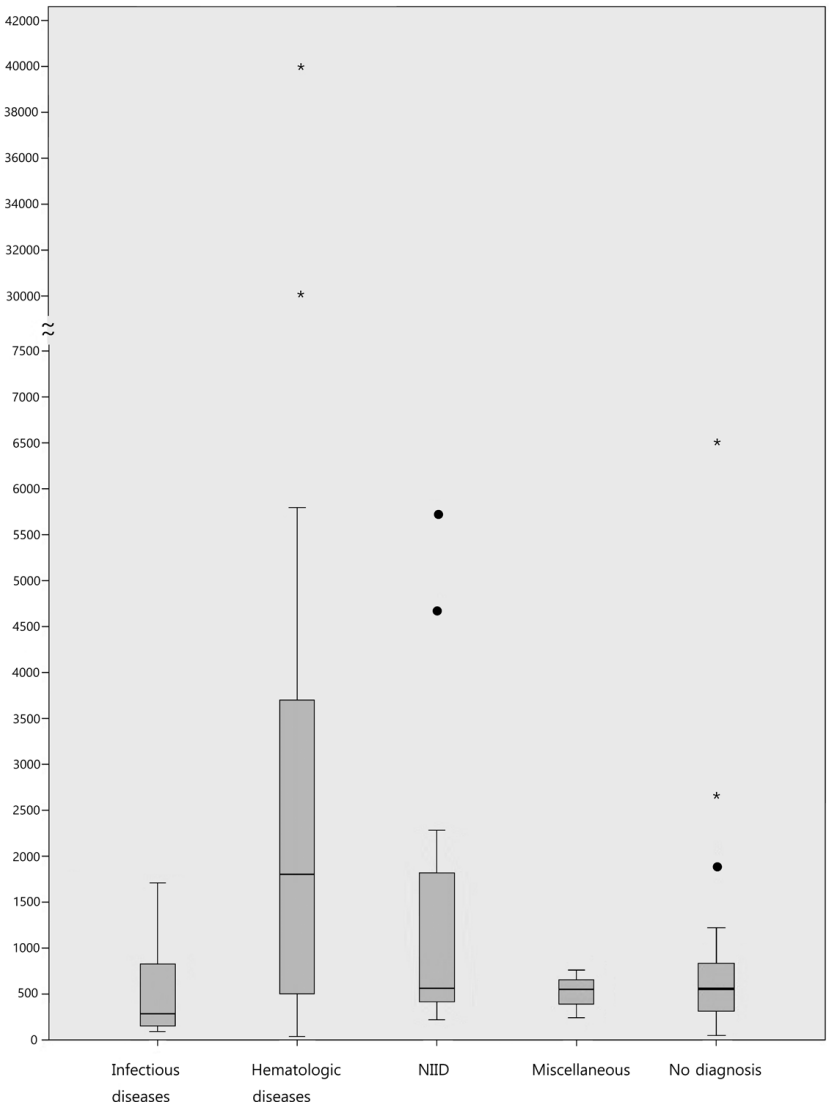
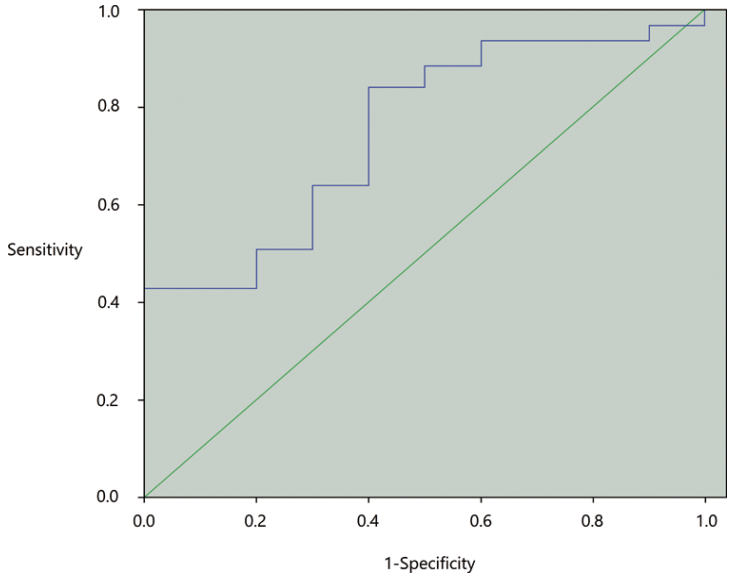


Fig. 2. Ferritin levels for each group. *extreme outlier $>$ Q3 + (IQR $\times$ 3), mild outlier $>$ Q3 + (IQR $\times$ 1.5).

groups, as well as between the infectious disease and NIID groups. However, no significant difference ($p = 0.25$) was found between the hematologic disease and NIID groups. When compared between the infectious disease and noninfectious disease groups (hematologic, NIID), the serum ferritin levels of the infectious disease group (282.4 (149.0–951.8) ng/mL) were significantly ($p = 0.02$) lower than those of the noninfectious disease group (863.5 (418.5–3327.6) ng/mL). Multiple regression analysis was performed to verify the statistical significance of serum ferritin levels for the differential diagnosis of FUO. Because the Kruskal–Wallis test revealed no significant findings other than that for serum ferritin, serum ferritin ($<$ 500 ng/mL), CRP ($>$ 6 mg/dL), and eosinopenia ($<$ 40/mm^3) were used for multiple regression analysis as known discrimination factors in FUO [11]. Serum ferritin showed marginal statistical significance in distinguishing between infectious and noninfectious diseases (hematologic, NIID) ($p = 0.06$; Table 4).

When the serum ferritin levels of the 48 patients for whom a final diagnosis was made were compared between the infectious disease and other groups (hematologic diseases, NIID, other diseases), the optimal cutoff value was found to be 537 ng/mL, with an AUROC of 0.73 (95% CI, 0.55–0.91), sensitivity of 63.2%, specificity of 70%, positive predictive value of 88.9%, and negative predictive value of 33.3%.



Characteristics	Values
AUROC	0.75
p-value	0.02
Cutoff value	561 ng/mL
Sensitivity	60%
Specificity	70%
PPV	81.8%
NPV	36.8%
95% CI*	0.58–0.91

*CI = confidence interval.

Fig. 3. ROC curve and optimal cutoff value of ferritin for noninfectious diseases [hematologic diseases, noninfectious inflammatory diseases (NIID)].

3.5. Ferritin as a predictor of the final diagnosis in serological tests

Of the 73 patients whose ferritin levels were measured, 43 had high serum ferritin levels ($\geqslant$ 500 ng/mL). Of the patients with ferritin levels above 1800 ng/mL, 12 patients had final diagnoses, including hemophagocytic syndrome (3 cases), adult-onset Still's disease (3 cases), lymphoma (2 cases), 1 case each of leukemia (acute lymphocytic leukemia) and hypereosinophilic syndrome, Rosai–Dorfman syndrome, and Kikuchi–Fujimoto disease. Statistical analysis of ferritin levels was performed for the infectious disease, hematologic disease, and NIID groups expected to show homogeneity among the 73 patients (Fig. 2). The optimal serum ferritin cutoff for prediction of a noninfectious disease (hematologic disease, NIID) in patients with FUO was 561 ng/mL. AUROC was 0.75 (95% CI, 0.58–0.91), with a sensitivity of 60%, a specificity of 70%, a positive predicted value of 81.8%, and a negative predicted value of 36.8% (Fig. 3).

4. Discussion

Fever is one of the most common symptoms indicative of a disease. The diagnosis rate of FUO remains so low that studies on effective prediction methods are still required. Although diagnostic methods using a specific algorithm have been proposed to minimize unnecessary tests in patients with FUO [4,14,15], a universal test has not yet been developed. In previous studies, the causes of FUO have been classified as infectious diseases, malignancies, NIID, and others [1, 3,4]. Most of the diseases classified as malignancies were hematologic malignancies such as Hodgkin's and non-Hodgkin's lymphoma and leukemia, along with a small number of solid cancers. Excluding a small number of solid cancers that are not associated with an increase in serum ferritin levels, and using serological tests as a classification without homogeneity for diagnosis, cases in the present study were divided into infectious diseases, hematologic diseases, NIID, and other undiagnosed cases to evaluate the use of serum ferritin for FUO diagnosis.

Our findings suggest that other serologic test indices excluding serum ferritin levels were inadequate for differentiation among individual disease groups. No differences in ESR, CRP, WBC fraction, or platelets were identified among infectious diseases, hematologic diseases, and NIID. Although Efstathiou et al. suggested that low ferritin concentrations ($<$ 500 ng/mL), eosinopenia ($\leqslant$ 40/mm^3), and high CRP (CRP $>$ 6 mg/dL) were associated with infectious diseases [11], there were no differences in CRP or eosinopenia between infectious and other diseases in our study. In Efstathiou's study, many relatively acute bacterial infections were included in 34 cases of infectious diseases, including 10 cases of infective endocarditis, 2 of osteomyelitis, and 1 of abdominal infection. Increases in CRP levels and eosinopenia (a marker of sepsis) during acute bacterial infection may also have been significant. However, based on our results, increases in CRP or eosinopenia may not be generalized to infectious diseases, such as tuberculosis or viral infections. In multiple regression analysis, the serum ferritin concentration showed marginal significance for discriminating between infectious and noninfectious disease ($p = 0.06$). If the sample size had been larger, the finding might have been statistically significant. In our study, which included different regions and races of subjects, serum ferritin was confirmed as a useful index for differentiation of infectious diseases, hematologic diseases, and NIID. Although serum ferritin may be increased in patients with fever, such an increase might become a factor in differential diagnosis of FUO rather than an acute-phase reactant, considering that the diagnosis criterion for FUO is a fever lasting longer than 3 weeks. While there were differences in the median values of hematologic diseases and NIID, these were not statistically significant (Mann-Whitney test). According to the data in Fig. 2, this may be due to the fact that the overall distribution of ferritin levels did not differ between these two groups, with the exception of a few cases of hematologic diseases that exhibited extremely high ferritin levels.

Interest in utilization of serum ferritin as a clinical tool for diagnosis of human diseases has increased [16, 17]. Since patients with hematologic malignancies such as Hodgkin's disease and acute leukemia have a reduced cellular immunity level and increased serum ferritin levels, serum ferritin is thought to be associated with immunity [18]. In addition, serum ferritin is related to inflammation and may be increased in the presence of chronic inflammation, such as chronic kidney disease, rheumatoid arthritis, or other autoimmune diseases. During chronic inflammation, such as hematologic malignancy or autoimmune diseases, the body produces hepcidin in the liver as a defense mechanism so that neither pathogens nor tumor cells can utilize serum iron by suppressing intestinal absorption and sequestration of iron in the macrophage, producing a relatively iron-deficient state, which is reflected by an increase in serum ferritin [19–21]. Therefore, our data suggest that serum ferritin may be a useful index for differentiation of infectious and noninfectious (hematologic disease or NIID) diseases in the treatment of patients with FUO. In this respect, serum ferritin has the advantage of decreasing the number of unnecessary tests and helping to exclude infectious disease before immunosuppressive treatment in NIID.

This study has several limitations. First, the results were obtained at a single hospital, and there is a high probability of selection bias. These results should be confirmed by studies at multiple institutions due to the possibility of region-specific differences. Secondly, it is possible that not all patients with FUO were included since the causes of some patient's fever were subsequently identified in a retrospective study based on diagnoses registered in the medical records. Third, the overall sample size was reduced since of the 77 patients, 8 had other diseases and 25 were not diagnosed. Fourth, some portion without clear boundaries between NIID and hematologic diseases was classified by the judgment of the investigator. Previous articles included cases of granulomatous disease, Crohn's disease, subacute thyroiditis, and Kikuchi-Fujimoto disease in NIID, depending on the investigators. Fifth, procalcitonin, which was recently used as an index of infectious disease, and glycosylated ferritin (known to be useful for diagnosis of adult-onset Still's disease) were not included in the present study since measurements of these two factors are difficult. Hence, additional studies are required. Sixth, we included only serum ferritin measured within 7 days of hospitalization, although the ferritin level can fluctuate with time. This could be a possible source of participant misclassification, as a single serum ferritin measurement may not be enough to reveal disease characteristics. In the future, additional validation studies based on a planned protocol are needed.

The diagnosis of FUO can be difficult for both patients and their physicians. Depending on the experience and qualifications of the treating physicians, time to reach a diagnosis can vary. In this study, we report that increased serum ferritin levels ($>$ 561 ng/mL) in patients with FUO corresponded to a low probability of

the presence of an infectious disease and a high probability of a hematologic disease or NIID. Thus, serum ferritin may in future be utilized to facilitate diagnosis.

5. Funding

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