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BRIEF REPORT

Ferritin to Erythrocyte Sedimentation Rate Ratio: Simple Measure to Identify Macrophage Activation Syndrome in Systemic Juvenile Idiopathic Arthritis

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Objective. Macrophage activation syndrome (MAS) is a life-threatening complication of systemic juvenile idiopathic arthritis (sJIA). Early diagnosis is critical. Classification criteria for MAS in sJIA perform less well in the setting of cytokine-directed therapies. The goal herein was to explore a simple ratio of serum ferritin to the erythrocyte sedimentation rate (ESR) for diagnosis of MAS in the setting of sJIA, and to assess ferritin alone as a screening tool for identifying MAS of multiple etiologies.

Methods. Data from a large international cohort of sJIA patients with and without MAS, and from hospitalized patients with systemic infection (SI), were assessed for the ferritin:ESR ratio and ferritin alone to identify MAS among sJIA patients. Moreover, data from a smaller cohort of MAS patients associated with multiple etiologies and febrile hospitalized controls were explored. For both cohorts and controls, receiver operating characteristic curves (ROCs) for the ferritin:ESR ratio and ferritin alone were constructed, and areas under the curves (AUCs) were calculated. The Youden index was used to determine the optimal ferritin:ESR ratio and ferritin alone cut points for diagnosis.

Results. A ferritin:ESR ratio of 21.5 was 82% sensitive and 78% specific for diagnosing sJIA-MAS versus active sJIA without MAS. Ferritin alone with a set sensitivity of 95% (screening tool) had an 89.3% specificity of identifying all-cause MAS versus febrile hospitalized children.

Conclusion. The ferritin:ESR ratio is a practical tool for diagnosing MAS among sJIA patients, and serum ferritin alone is a remarkable screening tool for identifying MAS among febrile hospitalized children.

INTRODUCTION

Macrophage activation syndrome (MAS) is a form of secondary hemophagocytic lymphohistiocytosis (sHLH) that complicates rheumatologic disorders. MAS is a potentially life-threatening condition, most commonly identified in children with systemic juvenile idiopathic arthritis (sJIA) and, to a lesser degree, in the adult equivalent, adult-onset Still disease (AOSD) (1). MAS is characterized by a dysregulation of the immune response, with a continuous activation and expansion of T lymphocytes and macrophages leading to a cytokine storm and ultimately resulting in multiorgan system failure (2).

Although MAS has been known to complicate other rheumatic disorders, specifically systemic lupus erythematosus (SLE) and Kawasaki disease (KD), much of the knowledge regarding the pathophysiology, clinical presentation, and treatment is derived from sJIA cohorts. The prevalence of MAS within the sJIA population is estimated to be 10%; however, reports suggest that the number of sJIA patients with subclinical MAS may be as high as 40% (3). sJIA and MAS share many clinical and laboratory features, and early recognition of MAS is crucial because timely treatment is important for survival.

Diagnostically, MAS is similar to sHLH in that presenting features include high unremitting fever, hyperferritinemia, pan-

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cytopenia, hepatosplenomegaly, and hypofibrinogenemia. Both conditions can be associated with other laboratory abnormalities, including elevated D-dimers, liver enzymes, and triglycerides. Soluble interleukin (IL)-2 receptor α-chain (sCD25) may be elevated, but testing is often not available at an on-site laboratory and therefore is not routinely done at the time of diagnosis. Bone marrow biopsy is often inconclusive. Although histopathology reveal characteristic increased hemophagocytic activity with positive CD163 (histiocyte) staining, this feature is often not present in initial stages nor is it highly sensitive or specific for MAS (4).

A major diagnostic obstacle is the absence of a single pathognomonic feature. Furthermore, the overlapping clinical and laboratory features MAS shares with other inflammatory diseases make universal diagnostic criteria near impossible. Using real patient data and comparable controls from a cohort of 1100 subjects in 33 countries, classification criteria for MAS in patients with sJIA were developed and published in 2016. The criteria proved to be both sensitive (0.73) and specific (0.99). In any febrile patient with confirmed or suspected sJIA, a diagnosis of MAS requires a serum ferritin level greater than 684 ng/ml plus any two of the following: platelet count 181 × 10^9/L or less, aspartate aminotransferase of more than 48 units/L, trigylceride greater than 156 mg/dl, or fibrinogen 360 mg/dl or lower (5). Unlike sCD25, these few labs are relatively inexpensive and usually readily available. The criteria have been validated in sJIA and applied to AOSD patients (5,6), but they may not prove to be the most accurate diagnostic tool for MAS in other systemic inflammatory conditions like SLE or KD. Moreover, in the setting of biologic therapies for sJIA (eg, targeting IL-1 or IL-6), these criteria perform less well (7). Other more complicated criteria have been proposed for identifying sHLH (primarily in the setting of cancer) (8), but a quick and easy way of diagnosing sHLH/MAS is needed.

A significant rise in serum ferritin (eg, greater than 10000 ng/ml) in the setting of a hospitalized febrile patient is a simple screening tool for sHLH/MAS. Although the ferritin levels usually rise in cases of sHLH/MAS, the ESR, although initially elevated as a nonspecific sign of inflammation, may be surprisingly low. The fall in ESR occurs secondary to fibrinogen (a major driver of the ESR) degradation as part of the consumptive coagulopathy, and decreased synthesis that is due to liver dysfunction, that occur in sHLH/MAS (2). Based on this, the ratio of ferritin to ESR is expected to rise in MAS. Gorelik et al reported that a ferritin:ESR ratio [ferritin (ng/ml) divided by ESR (mm/hr)] of greater than 80 showed a sensitivity and specificity of 100% in distinguishing MAS from new-onset sJIA without MAS in a small (n = 28) cohort (9). Thus, the ferritin:ESR ratio shows promise as an inexpensive and quick calculation to rapidly diagnose MAS, prevent delay in treatment, and improve outcomes. Therefore, we evaluated the ferritin:ESR ratio, and ferritin alone, as diagnostic and/or screening tests for the presence of sHLH/MAS in a large multinational cohort of sJIA patients (n = 524) and in a cohort of pediatric sHLH patients (n = 52) with multiple underlying etiologies.

PATIENTS AND METHODS

Data were reviewed from a multinational study of patients with sJIA-MAS (n = 362), sJIA flare without MAS (n = 404), and hospitalized systemic infections (SIs) (n = 345) (same data used to develop the American College of Radiology (ACR)–European League Against Rheumatism (EULAR) sJIA-MAS criteria for sJIA-MAS) (5). Patients without documented ESR and ferritin were excluded, leaving 262 sJIA-MAS, 262 sJIA flare, and 93 patients with SI.

In addition, a second patient population was evaluated to explore the ability of the ferritin:ESR ratio not only to distinguish patients with sJIA-MAS from patients with sJIA flare without MAS but to also distinguish sHLH/MAS with any potential underlying etiology from febrile hospitalized patients without sHLH/MAS. The electronic medical records (EMRs) at Children's of Alabama (CoA) were searched for all patients diagnosed with sHLH/MAS (ICD9-288.4, ICD10-D76.1) from January 2008 through December 2016 regardless of underlying etiology. All primary HLH patients were excluded. All included patients satisfied at least one of five published sets of criteria: HLH-2004 (10), HLH-2009 (11), SLE MAS (12), sJIA MAS-2016 (5), and HScore (8). The EMR was searched for age and sex-matched comparator patients hospitalized over the same time frame with fever and had both ferritin and ESR tested. For patients with multiple hospital admissions, data from their first visit was reported. For all patients, the first ferritin tested during the hospital admission was documented with the closest ESR measured within a timeframe of 48 hours before or after the ferritin. Patients were excluded for the following reasons: sickle cell disease, hemochromatosis, receipt of multiple blood transfusions prior to the measurement of ferritin, receipt of intravenous immunoglobulin prior to ESR measurement, age less than 1 year, and sJIA with MAS. There were 52 sHLH/MAS patients and 159 febrile comparator patients identified (Supplemental Table 1).

Table 1. Sensitivity and specificity of the cut points for ferritin:ESR ratio and ferritin alone in cases of sJIA-MAS vs active sJIA and sJIA-MAS vs SI

	sJIA-MAS vs Active sJIA	sJIA-MAS vs SI
Ferritin:ESR cut point	21.5	11.3
	Sensitivity 82%	Sensitivity 91%
	Specificity 78%	Specificity 93%
Ferritin cut point (ng/ml)	1,045	396.6
	Sensitivity 84%	Sensitivity 92%
	Specificity 66%	Specificity 95%

Abbreviation: ESR, erythrocyte sedimentation rate; MAS, macrophage activation syndrome; SI, systemic infections; sJIA, systemic juvenile idiopathic arthritis.

Table 2. Comparison between the ferritin:ESR ratio and the ACR-EULAR criteria for diagnosing sJIA-MAS

	Ferritin:ESR	ACR-EULAR sJIA-MAS Criteria
AUC	0.87	0.86
Sensitivity	82%	73%
Specificity	78%	99%
Sensitivity at 99% specificity	46%	73%

Abbreviation: ACR, American College of Rheumatology; AUC, area under the curve; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; MAS, macrophage activation syndrome; sJIA, systemic juvenile idiopathic arthritis.

Using the ACR-EULAR multinational data, patients with sJIA-MAS were compared with patients with sJIA without MAS and with patients with SI; additionally, using the CoA EMR data, patients with sHLH/MAS were compared with patients with febrile illness. Receiver operating characteristic curves (ROCs) for the ferritin:ESR ratio and ferritin alone were constructed, and areas under the curves (AUCs) were calculated with 95% confidence intervals. The Youden index was used to determine the optimal ferritin:ESR ratio and ferritin alone cut points for diagnosis. Cut points that produced 95% sensitivity were identified, and the corresponding specificity was determined to evaluate the utility of the ferritin:ESR ratio and ferritin alone as screening tests for sHLH/MAS.

RESULTS

Comparing sJIA-MAS with sJIA flare without MAS, the multinational data showed the ferritin:ESR ratio, with an optimal cut point value according to the Youden index of 21.5, had sensitivity of 82% and specificity of 78% [AUC: 0.87 (0.84-0.90)] (Supplemental Figure 1A, Table 1). Ferritin alone, with a cut point of 1045 mg/dl, had sensitivity of 84% and specificity of 66% (AUC: 0.81 [0.78-0.84]) (Supplemental Figure 1B, Table 1). These results were comparable to the ACR-EULAR sJIA-MAS criteria, which had an AUC of 0.86 with a lower sensitivity (73%) but a higher specificity of 99% (Table 2).

When assessing performance at a 99% specificity for use as a diagnostic test, the ferritin:ESR ratio yielded 46% sensitivity, whereas the ACR-EULAR sJIA-MAS criteria set a 99% sensitivity and resulted in 73% sensitivity (Table 2). When assessing performance at the 95% sensitivity level for use as a screening test for sJIA-MAS, the ferritin:ESR ratio at a cut point of 4.9 or greater had specificity of 41%, whereas the ferritin at a cut point of 225 ng/ml or more had specificity of 31% (Table 3). Therefore, for MAS-sJIA versus active sJIA, ferritin alone does not discriminate as well as the ferritin:ESR ratio.

Comparing sJIA-MAS cases versus infections using the data from the multinational study, a ferritin:ESR ratio at a cut point of 11.3 had a sensitivity of 91% and specificity of 93% [AUC: 0.95 (0.92-0.97)] (Supplemental Figure 2A, Table 1)). Ferritin alone, with a cut point of 396.6 ng/ml, was found to have sensitivity of 92% and specificity of 95% [AUC: 0.97 (0.95-0.98)] (Supplemental Figure 2B, Table 1). When assessing performance at 95% sensitivity in order to evaluate their utility as screening tests, the ferritin:ESR ratio at a cut point of 4.9 or greater had specificity of 78%, whereas the ferritin alone at a cut point of 225 mg/dl or more had specificity of 85% (Table 3). Therefore, ferritin alone discriminated better than the ferritin:ESR ratio between patients with sJIA-MAS and febrile patients with infection.

Comparing patients with sHLH/MAS with variable underlying etiologies versus febrile hospitalized patients (Supplemental Table 1), the ferritin:ESR ratio, with the previously defined cut point of 11.3 (for MAS vs SI), yielded sensitivity of 92% and specificity of 86% [AUC 0.96 (0.93-0.99)] (Supplemental Figure 3A). When using the optimal cut point obtained by the Youden index from these current data, which was 14.4, the sensitivity remained the same at 92% and specificity improved to 89%. Using ferritin alone, a cut point of 969 ng/ml has a sensitivity of 90% and a specificity of 96% [AUC is 0.98 (0.95-0.99)] (Supplemental Figure 3B). When assessing performance at 95% sensitivity, the ferritin:ESR ratio at a cut point of 4.32 or greater had

Table 3. Specificity of ferritin:ESR ratio and ferritin alone at 95% sensitivity in cases of sJIA-MAS vs sJIA, sJIA-MAS vs SI, and all cause MAS vs febrile patients (CoA data)

Comparison	Laboratory Test	Specificity at 95% Sensitivity	Cut Point
sJIA-MAS vs sJIA flare (ACR-EULAR data)	Ferritin:ESR	41.1%	≥4.9
	Ferritin alone	30.7%	≥225
sJIA-MAS vs SI (ACR-EULAR data)	Ferritin:ESR	77.9%	≥4.9
	Ferritin alone	85.2%	≥225
All cause MAS vs Fever (CoA data)	Ferritin:ESR	65.4%	≥4.32
	Ferritin alone	89.3%	≥627

Abbreviation: ACR, American College of Rheumatology; CoA, Children's of Alabama; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; MAS, macrophage activation syndrome; SI, systemic infections; sJIA, systemic juvenile idiopathic arthritis.

a specificity of 65%, whereas the ferritin alone at a cut point of 627 ng/ml or more had specificity of 89% (Table 3). Thus, the ferritin alone was a good screening test for identifying all causes of sHLH/MAS when compared with febrile hospitalized patients as comparators.

DISCUSSION

Several criteria have been proposed to diagnose HLH/MAS. One of the most commonly employed guidelines is the HLH-2004 criteria (10). The HLH-2004 guidelines were initially intended to diagnose familial HLH; thus, they are often too restrictive for early diagnosis of sHLH/MAS. In addition, they are not timely when early diagnosis and treatment are critical for survival. It might take several days to get all the labs reported, especially sCD25 and natural killer cell function, typically sent to a remote lab. Moreover, bone marrow biopsy might be delayed or not done because of the patient's clinical condition. The HLH-2004 guidelines were previously shown to perform poorly in identifying MAS among a large cohort of sJIA patients (1). The HScore is another tool used to identify sHLH/MAS, but it is cumbersome to perform and requires several labs, including bone marrow aspiration, to identify hemophagocytosis (8). Moreover, it was originally developed from data of patients with primarily malignancy-related HLH. There has also been a trend to establish diagnostic guidelines for MAS complicating different underlying rheumatic disorders like systemic SLE (13) and sJIA (14). Although these are more specific and tailored to the underlying disease, they might not be as helpful for newly diagnosed cases presenting with MAS where the disorder is not yet diagnosed. Therefore, one set of criteria for all causes of sHLH/MAS that is timely and feasible will be valuable.

The current study objective was to find simplistic and timely criteria using labs that would be readily available in most hospitals within 24 hours. In addition to establishing a sHLH/MAS diagnosis, we explored identifying a screening test to raise an alarm for the possibility of MAS. Results from a simple screen will allow clinicians to proceed to further investigations to confirm the sHLH/MAS diagnosis or to help exclude a diagnosis of sHLH/MAS for the meantime.

Two relevant, inexpensive, and timely labs are the serum ferritin and ESR. Typically, the ferritin level rises in cases of sHLH/MAS, whereas the ESR drops. A falling ESR suggests fibrinogen consumption and decreased production, and it has been established as an early lab finding in sJIA complicated by MAS (15). Although fibrinogen is an acute phase reactant, it gets consumed as the coagulopathic state of MAS ensues. In comparison, the serum ferritin level is not expected to be markedly raised in sJIA flare (not greater than 684 ng/ml per the ACR-EULAR criteria) (5), but the ESR is usually notably increased, driven by inflammation. Therefore, the higher the ratio of ferritin to ESR, the higher the likelihood the case is complicated by MAS (14). In 2013, Gorelik et al reported a case-control study of 28 patients with sJIA, 7 of whom developed MAS, and matched them with age-, race-, and gender-similar controls (n = 30). A ferritin:ESR greater than 80 showed a sensitivity and specificity of 100% in distinguishing MAS from new-onset sJIA. When the ratio was lowered to more than 37, the sensitivity remained 100% while the specificity decreased to about 90% (9). This appeared promising for distinguishing MAS from sJIA flare in this small cohort.

Herein, using a large sJIA cohort, the AUC was calculated to find the optimal cut point of ferritin:ESR ratio and ferritin alone that differentiates between sJIA-MAS versus active sJIA, sJIA-MAS versus patients with SI, and MAS versus both. The ferritin to ESR ratio was better than ferritin alone in differentiating the sJIA-MAS group from the active sJIA flare with a cut point of 21.5. In the study by Gorelik et al, the ferritin:ESR ratio was superior to ferritin alone, sCD25, and follistatin-like protein 1 in discriminating MAS from new-onset sJIA. In their study, a ferritin:ESR ratio greater than 80 provided statistically optimal sensitivity and specificity (9). The discrepancy in the cut points between our study and theirs could be attributed to the small numbers (n = 28 with sJIA, 7 with MAS) in their study. In our study, ferritin alone was slightly better than the ferritin:ESR ratio in differentiating sJIA-MAS patients from patients with SI with a cut point of 396.6 ng/ml. However, between the two approaches, the sensitivities and specificities were comparable.

Our results have further shown that to differentiate sJIA-MAS from sJIA flare, ferritin alone does not discriminate as well as the ferritin:ESR ratio. Conversely, ferritin alone discriminated slightly better than the ferritin:ESR ratio between patients with sJIA-MAS and febrile SI patients. Thus, serum ferritin alone can be used as an initial screening tool for MAS in febrile hospitalized patients to consider obtaining other MAS markers (eg, transaminases, lactic acid dehydrogenase, triglycerides, D-dimers, etc).

In addition to helping to differentiate sJIA-MAS from sJIA flare without MAS, we explored the utility of the ferritin:ESR ratio in discriminating sHLH/MAS of multiple etiologies from febrile hospitalized controls without MAS in a separate cohort. Interestingly, the ferritin:ESR ratio performed quite well in distinguishing MAS associated with multiple conditions from hospitalized febrile children without MAS. However, the ferritin alone performed even better. This furthers an argument to be made for obtaining an initial screening serum ferritin for all hospitalized febrile patients (2).

In summary, the serum ferritin:ESR ratio (with a cut point of 21.5 or greater) is a simple, timely, sensitive, and reasonably specific tool that distinguishes sJIA-MAS from active sJIA without MAS. This ratio performs comparably to the ACR-EULAR criteria for the diagnosis of MAS but with lower specificity. Nevertheless, serum ferritin alone is sufficient to screen for MAS from all causes among febrile hospitalized patients (cut point 627 ng/ml or greater). We suggest that other centers validate the ferritin:ESR ratio and ferritin alone as diagnostic and screening tools for MAS in different patient populations.

AUTHOR CONTRIBUTIONS

All authors drafted the article or revised it critically for important intellectual content; all authors gave final approval of the version of the article to be published.

Study conception and design. Cron.
Acquisition of data. Eloseily, Minoia, Crayne, Ravelli, Cron.
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