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# A Validated Scale for Assessing the Severity of Acute Infectious Mononucleosis

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## Abstract

**Objective:** To develop a scale for the severity of mononucleosis (SOM).

**Study design:** One to 5 percent of college students develop infectious mononucleosis annually, and about 10% meet criteria for chronic fatigue syndrome (CFS) 6 months following IM. We developed a SOM scale based on a review of the literature. College students were enrolled, generally when they were healthy. When the students developed IM an assessment was made as to the severity of their IM independently by two physicians using the SOM scale. This scale was correlated with corticosteroid use and hospitalization. Six months following IM an assessment is made for recovery from IM or meeting one or more case definitions of CFS.

**Results:** 126 SOM scales were analyzed. The concordance between the two physician reviewers was 95%. All three hospitalized subjects had SOM scores ≥2. Subjects with SOM scores of ≥1 were 1.83 times as likely to be given corticosteroids. Students with SOM scores of 0 or 1 were less likely to meet more than one case definition of CFS six months following IM.

**Conclusions:** The SOM scale has interobserver, concurrent and predictive validity for hospitalization, corticosteroid use and meeting criteria for CFS 6 months following IM.

Chronic fatigue syndrome (CFS), or systemic exertion intolerance disease (SEID) is a complex condition involving severe fatigue and disabling cognitive and musculoskeletal symptoms [1–4]. Six months following IM, ~10% of adolescents or young adults meet criteria for CFS [5–7].

One to 5% of college students develop acute infectious mononucleosis (IM) annually [8]. In an attempt to understand why about 10% of young adults meet criteria for CHS following IM, two previous studies related the severity of the acute illness (IM) to the development of

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CFS [9,10]. In one study, however, the specifics of the severity measurements were not detailed [9], and in the other, the scale used was not validated for this use [10]. We are aware of two other tools that have been used to measure the severity of acute IM, but these scales also have not been validated either in general or for IM specifically [11,12]. As part of a study to assess risk factors for the development of CFS following IM, we developed and then attempted to validate a scale for rating the severity of IM, by first reviewing the literature available prior to beginning our study for risk factors for the severity of acute IM [13–18]. We excluded one study that involved young Chinese children [13]. Chretien et al showed that gastrointestinal symptoms such as anorexia, nausea or vomiting, and palatal petechiae correlated with prolonged recovery from IM.[14] Tattevin et al reported on patients hospitalized with acute IM with severe hepatitis, dysphagia, hemophagocytic lymphohistiocytosis, a painfully enlarged spleen, airway obstruction, meningoencephalitis, myocarditis, hemolytic anemia, or pleural effusion; thus any of these signs or symptoms that lead to hospitalization were considered a severe manifestation of IM.[15] Macsween et al have shown a significantly longer duration of fatigue following IM in females who could not walk 100 meters at the time that their acute illness was most severe.[16] Jason et al and Katz et al found that days spent in bed since IM, along with autonomic dysfunction 2 months after the diagnosis, was associated with post-infectious CFS at six months.[17], [18] We used all these data to develop a scale for the severity of infectious mononucleosis (SOM)

## METHODS

Our ongoing study to examine risk factors for developing CFS following IM has three stages. In Stage 1, we attempt to enroll students who are generally healthy. When the students develop IM, they enter Stage 2 of the study. Six months following IM, students are assessed for recovery vs nonrecovery (Stage 3).

We rated 126 students who developed IM (Stage 2) at the Northwestern University Health Center (NUHS) from Dec 2013 through Mar 2017. There were 56 males and 70 females, ranging in age from 18 – 23 years. Students enrolled in the study who were diagnosed with IM were treated by NUHS physicians. The diagnosis of IM was made either via a positive monospot test, a positive viral capsid antigen IgM test or a positive viral capsid antigen IgG test in the presence of a negative antibody to Epstein-Barr nuclear antigen. Records of the acute clinic visit(s) were reviewed separately by two independent study physicians not involved in the clinical care of the student at the time IM was diagnosed; each independent study physician separately completed the SOM scale for each of the 126 subjects. All disagreements were resolved by discussions between the two physicians.

Six months following IM, all of the students were contacted by phone and /or email and assessed for recovery vs non-recovery. An approximately 1:1 ratio of those who were still symptomatic vs those who endorsed completely recovery were then brought in for a comprehensive medical evaluation (Stage 3). Students were then classified as recovered or meeting one or more than one case definition of CFS. The 3 case definitions of CFS used were the Fukuda definition [1], the Canadian Consensus criteria [2,3] and the Institute of Medicine criteria for SEID [4]. The Fukuda criteria tend to be the least stringent. We characterized those who met >1 set of criteria for CFS as having *severe* CFS. Serum, plasma

and viable white blood cells are stored on each subject at each visit for future studies (cytokines, metabolomics and genomics). Plasma and serum are preserved at −80°C and pelleted viable white blood cells are preserved in liquid nitrogen.

Chi-square analyses were conducted using IBM SPSS version 21. Fisher exact tests were conducted for analyses where sample sizes of conditions were less than 5. Post-hoc risk ratios were calculated following Chi-Square tests.

This study was approved by the Institutional Review Boards of Northwestern University, DePaul University and the Stanley Mann Research Institute of the Ann & Robert H Lurie Children's Hospital of Chicago. All subjects provided written, informed consent at each stage of the study.

## RESULTS

Records pertaining to acute care visits for IM (n =126) were blindly reviewed by two independent study physicians; concurrence between scorers was 95%, thus showing the SOM scale to have *interobserver reliability*. Discrepancies generally were matters of judgment involving over or under interpretation of clinical findings (eg, scoring elevated transaminases without clinical symptoms as hepatitis) or double scoring a single sign or symptom (eg, counting trouble breathing due to a pleural effusion twice). All disagreements were resolved by discussions between the two physicians.

Of the 8 symptoms of severe IM identified from the literature (Table I), our subjects endorsed only 3: "Not able to leave home during worst symptoms," "Trouble breathing," and "GI symptoms." No subject had a bull neck or a cardiac or neurologic complication. Of the 9 remaining signs or symptoms of IM, we grouped together the symptom of "Trouble breathing" and "Pulmonary complications" due to small numbers and likely overlap. All items present in > 2 subjects are shown in Table 2.

There was a statistically significant association between severity of IM score and prescription of corticosteroids ($\chi^2$ [3, N = 126] = 11.55, $P < .01$). Of 56 participants endorsing 1 or more risk factors for severe IM, 31.4% were prescribed corticosteroids, whereas of 70 participants who did not meet any risk factors for severe IM, 17.2% were prescribed corticosteroids. Those who scored ≥1 on the severity of IM measure had 1.83 times the risk of being prescribed corticosteroids compared with those who had a score of 0 on the severity of IM measure.

There was also a significant association between severity of IM score and hospitalization ($\chi^2$ [3, N = 126] = 9.99, $p < 0.01$). Patients endorsing 2 or more risk factors for severe IM (N = 25) had a 12% risk of hospitalization, whereas patients who met 1 or fewer risk factors (N = 101) had no hospitalization. These data provide evidence of *concurrent validity* for the SOM scale, as the scale was able to identify those more likely to be hospitalized and prescribed corticosteroids, as physicians scoring the SOM scale played no role in the decision to hospitalize or prescribe corticosteroids.

Of the 65 participants evaluated 6 months after IM diagnosis, 52.3% (N = 34) did not meet any CFS case definition criteria, 27.7% (N = 18) met a single CFS case definition criterion, and 12.3% (N = 8) met the criteria for two or more CFS case definitions. An additional 7.7% (N = 5) participants were diagnosed with either lingering symptoms or idiopathic chronic fatigue, and could therefore not be classified as either recovered from mononucleosis or as meeting a case definition criteria. There was a statistically significant relationship between SOM score and CFS diagnosis ($\chi^2$ [6, N = 60] = 9.63, $p < 0.05$, V = .31). A higher SOM score increased the risk of a more severe CFS diagnosis (Table 3). At a SOM score of 2 or greater, the risk of meeting more than 1 case definition of CFS was 28.6%. At a SOM score of 1 or less, the risk of meeting more than 1 case criteria of CFS was 8.7%. Participants who had a SOM score of 2 or greater had 3.29 times the risk of meeting more than 1 case definition of CFS compared with participants who had a lower SOM score. A CFS diagnosis also trended towards a relationship with needing hospitalization ($\chi^2$ [2, N = 60] = 3.81, $p < 0.08$); 7.7% (N=2) of participants who met one or more case definition criteria were hospitalized, whereas no participant who did not meet a case definition criteria were hospitalized. No significant relationship between CFS diagnosis and being prescribed corticosteroids was identified ($\chi^2$ [2, N = 60] = 0.11, $p > 0.05$). Individual severity items were also examined for their association with case definition criteria (Table 2). Of these items, only GI symptoms and breathing difficulties were associated with meeting CFS case definition criteria.

## DISCUSSION

We developed a scale to rate symptoms and signs of IM in college students that is relatively easy to use, has high interobserver reliability and correlates with hospitalization, the likelihood of corticosteroids being prescribed, and development of *severe* CFS (i.e., subjects who met >1 set of standard criteria for CFS six months following IM). These findings partially corroborated some [9,10] but not all (e.g., [6]) data from adult studies of CFS following IM.

Several previous publications have rated the severity of IM. In one report, the details were not given [9]. In others, the scales, which appeared useful, were either not validated [10] or not validated specifically for use in IM [11,12]. In our study we developed a validated scale for rating IM.

Limitations of the present study include heterogeneity in evaluation at the time of diagnosis of IM because subjects received care by a variety of NUHS physicians who were not part of our study. Also, although the SOM scale correlated with corticosteroid use, hospitalization and the diagnosis of CFS, corticosteroid use and hospitalization were not statistically significantly associated with a diagnosis of CFS, possibly due to small sample size. Finally, the percentage of students who met at least one set of criteria for CFS 6 months following IM was higher than generally is reported, perhaps due to the fact that we were studying college students who often report a high level of background fatigue.

Our validated scale provides a simple, objective, reproducible measure for quantifying the severity of IM in young adult college students. Hopefully the SOM scale can be used to

guide future attempts at anticipatory guidance and/or prevention of some of the more serious consequences of IM by identifying individuals who at the time of diagnosis of IM are at risk for hospitalization or non-recovery six months following the diagnosis. The score could also be useful in a prospective study of benefit and risk of corticosteroid therapy or other interventions.

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## LIST OF ABBREVIATIONS

| | |
|---|---|
| **CFS** | chronic fatigue syndrome |
| **NUHS** | Northwestern University Health Service |
| **SEID** | systemic exertion intolerance disease |

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**Table 1.**

Severity of Infectious Mononucleosis Scale

Severe symptoms [a]:

_____ Pharyngitis to the point where can't swallow even liquids

_____ Headache so severe as to prompt an LP or neuroimaging

_____ Fever > 104ºF for > 2 weeks

_____ Fever > 101ºF for > 5 weeks

_____ Not able to leave home during worst symptoms

_____ Reduced walking distance during worst symptoms

_____ Trouble breathing

_____ GI symptoms (anorexia, nausea, vomiting: NOT Diarrhea alone)

Severe Physical Examination findings:

_____ Jaundice

_____ "Bull neck" (prominent, warm, tender bilateral cervical adenopathy with edema)

_____ Painfully enlarged spleen

_____ Painfully enlarged liver

_____ Palatal petechiae

Complications [b]:

_____ Cardiac (e.g., myocarditis)

_____ Hematologic (e.g., thrombocytopenia (<150,000/mm3), neutropenia (<1000/mm3), lymphopenia (<2000/mm3), hemolytic anemia, hemophagocytic lymphohistiocytosis)

_____ Neurologic (e.g., meningoencephalitis)

_____ Pulmonary (e.g., pleural effusion, pneumonitis)

[a] Each sign, symptom or complication present scores a 1

[b] Do not count the same sign or symptom more than once (e.g., if trouble breathing due to pleural effusion, count one or the other but not both)

**Table 2.**

Frequency of Severe Symptoms/Signs by Case Definition Criteria for CFS.

| Symptom | Participants who did not meet case definition criteria | Participants diagnosed by 1 criterion | Participants diagnosed by > 1 criteria | $\chi^2$(df) | p |
|---|---|---|---|---|---|
| GI symptoms | 26.5% (9) | 22.2% (4) | 75.0% (6) | 8.11 (2) | .01 |
| Hematologic complications | 26.5% (9) | 16.7% (5) | 12.5% (1) | 0.90 (2) | .30 |
| Trouble breathing/pulmonary complications | 2.9% (1) | 11.1% (2) | 25.0% (2) | 4.32 (2) | .035 |
| Tender, enlarged spleen | 2.9% (1) | 5.6% (1) | 0.0% (0) | 0.57 (2) | .50 |

**Table 3.**

Association of Risk Factors Scores at Diagnosis of IM and Case Definition Criteria of CFS.

| | ≤1 Risk Factor (N=46) | ≥2 Risk Factors (N=14) |
|---|---|---|
| No CFS Case Definition | 60.9% (28) | 42.9 % (6) |
| 1 CFS Criterion | 30.4% (14) | 28.6% (4) |
| >1 CFS Criterion | 8.7% (4) | 28.6% (4) |