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USE OF THE MULTI-ORGAN DYSFUNCTION SCORE AS A TOOL TO DISCRIMINATE DIFFERENT LEVELS OF SEVERITY IN UNCOMPLICATED *PLASMODIUM FALCIPARUM* MALARIA

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Abstract. The usual criteria for severe malaria are not always sufficient to identify patients who subsequently develop this disease. The multi-organ dysfunction score (MODS) was assessed in 22 patients with uncomplicated *Plasmodium falciparum* malaria to test its usefulness in discriminating different severity levels. The MODS on admission was highly correlated with the baseline concentration of tumor necrosis factor-α ($r = 0.83$, $P < 0.001$) and the duration of symptoms after admission ($r = 0.54$, $P = 0.01$). The MODS was also correlated with parasite count ($r = 0.52$, $P = 0.014$), parasite clearance time ($r = 0.54$, $P = 0.009$), and fever clearance time ($r = 0.58$, $P = 0.005$). The above correlations remained significant after controlling for the initial parasitemia ($P = 0.03$ and 0.005). The MODS is simple and easy to apply and needs a recording time of less than three minutes. Thus, this score might provide a quantitative approach for determining severity in *Plasmodium falciparum* malaria.

INTRODUCTION

Malaria occurs throughout most of the tropical world and remains a major cause of morbidity and mortality in these regions. *Plasmodium falciparum* malaria can manifest itself with a variable degree of severity, ranging from asymptomatic infection to multi-organ involvement and death. This is determined by both host factors, including the immunity, age, and geographic location of the patient and parasite factors. The pathophysiology of *P. falciparum* malaria is complex and still incompletely understood. Parasite multiplication and cytoadherence are the main determinants of severe manifestations. The sequestration of a critical parasite biomass leads to organ dysfunction that is aggravated by tissue hypoxia as a consequence of erythrocyte destruction.[1] Pro-inflammatory cytokines have shown to play an important role in these manifestations. Tumor necrosis factor-α (TNF-α) has been associated with severe malaria.[2–4] High levels of serum TNF-α were found in malaria patients with multi-organ involvement, particularly those with acute renal failure.[5]

From the clinical point of view, it is important to classify patients into different severity groups so that more resources may be allocated to patients at risk of dying. Patients with *P. falciparum* malaria are classified as having severe and complicated malaria if they fulfill one of the criteria defined by the World Health Organization, which include acute renal failure, pulmonary edema, cerebral malaria, and severe anemia.[6] However, there is a continuum between mild malaria and severe malaria and some patients might not have obvious severity signs on admission, but may very rapidly develop such signs. There have been attempts to identify this intermediate patient group with parasitologic and clinical criteria.[7] Nevertheless, there is no satisfactory classification to identify this gray zone of malaria.

The multi-organ dysfunction score (MODS) is widely used in European countries to assess disease severity in patients admitted to the intensive care unit independently of diagnosis.[8] Fourteen organ systems are evaluated on a daily basis during hospitalization, with four of them being optional. The grading depends on both clinical and laboratory data. Our objective was to identify different levels of severity within a group of patients with uncomplicated *P. falciparum* malaria using the MODS and to determine the correlation of this score with parameters such as levels of TNF-α and morbidity. In addition, we used a simplified MODS based mainly on clinical findings to determine its usefulness for malaria centers with limited laboratory facilities.

MATERIALS AND METHODS

Study site. The study was conducted at the Hospital for Tropical Diseases in Bangkok, Thailand, a research hospital and referral center for tropical diseases, between October 1, 2001 and January 30, 2002.

Study population. This prospective study included 22 consecutive patients 15 years of age and older with mild *P. falciparum* malaria. Diagnosis was defined by the presence of asexual forms of *P. falciparum* on blood smears. Mild malaria was defined by the absence of any of the severity criteria of the World Health Organization.[6,7] Most patients were of Thai (68%) or Burmese (27%) origin and came from the Thailand-Myanmar border area. We excluded 1) patients with previous malaria infection in the last 30 days before admission, 2) patients who were pregnant or lactating after childbirth, and 3) patients with proven systemic infection other than malaria. Twenty-one healthy, matched Thai volunteers served as controls for determination of serum levels of TNF-α.

Patients consent and ethical approval. Informed consent was obtained from all patients and controls. For underage children, a responsible family member or friend gave informed consent. The study was approved by the Ethical Committee of the Faculty of Tropical Medicine of Mahidol University (Bangkok, Thailand).

Clinical evaluation. Study physicians and nurses completed a structured questionnaire that included information about previous illness, current symptoms, and recent medications and performed a physical examination. Clinical signs and symptoms were recorded daily during the first week and then weekly.

MODS and the simplified MODS. The patient́s severity was assessed by using the multi-organ-dysfunction score (MODS) (Table 1) that evaluated 10 organ systems within the first 24 hours (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immune system, and central nervous system).[8] The additional four optional organ systems were not evaluated in

TABLE 1
Multi-organ dysfunction score (MODS) grading system*

1) Normal function, no further intervention necessary
2) Restricted function with clinical significance; organ function compensated using conventional therapy
3) Restricted function of considerable clinical importance; organ function compensated using maximal specific therapy
4) Restricted function of major clinical importance; organ function at time or permanently decompensated despite maximal specific therapy
5) Restricted function with poor prognosis; organ function constantly decompensated

* Adapted from Weiler and others.[8] The score of each organ system (heart, blood vessel, blood, respiratory system, metabolism, gastrointestinal system, liver, kidney and urinary tract, immunologic system, and central nervous system) is evaluated with a minimum score of 1 and a maximum score of 5. The sum of the single organ scores represent the MODS with a minimum of 10 points.

our series (skin, bone, connective tissue/endocrinology/pancreas, and peripheral nervous system).

The simplified MODS was based mainly on clinical data: packed cell volume and urine examination (urine dipstick for albumin and glucose) were the only laboratory data used; other organ systems were assessed by clinical findings such as heart rate for the heart; respiration rate and cyanosis for the respiratory system; anemia or icteric sclera for the blood; liver enlargement for the liver; nausea, vomiting, and diarrhea for the gastrointestinal system; dehydration, oliguria, and anuria for the kidney; and headache and mental changes for the central nervous system.

In both scoring systems, each organ system is classified in five stages (scores of 1 to 5) according to its functionality and the necessary therapeutic intervention. Normal function in all organ systems is reflected by a single organ score of 1 and a total score of 10.

Laboratory evaluation. Routine laboratory examinations (complete blood count, glucose-6-phosphate dehydrogenate status, total bilirubin, direct bilirubin, alkaline phosphatase, aspartate aminotransferase [AST], alanine aminotransferase [ALT], creatinine, blood urea nitrogen, albumin, and globulin) were performed on days 0, 7, 14, 21, and 28. All patients were participants of other treatment studies conducted at the Hospital for Tropical Diseases in Bangkok. Blood for determination of TNF-α levels was collected in serum tubes before treatment was started. Samples were aliquoted and stored at –70°C. Measurements of TNF-α levels were performed with an enzyme-linked immunosorbent assay that had a sensitivity of less than 10 pg/ml (TNF-α Diaclone test kit DC 850090192; Diaclone Besançon, France). This kit recognizes both free and receptor-bound TNF-α. All samples, including serum samples of healthy control subjects, were tested in duplicate.

Thick and thin blood smears were stained with 10% Giemsa. Parasite counts were determined every 12 hours until they were negative, then once a day until discharge and weekly until day 28.

Definitions. Parasite clearance time (PCT) was the duration in hours for the parasitemia to decrease below the level of detection. Fever clearance time (FCT) was the duration in hours for the temperature of a patient to decrease to 37°C and remain there for at least 24 hours. Temperature was measured orally in all patients. Other parameters measured were a decreased hemoglobin concentration (< 14 g/dl in males and < 12 g/dl in females), thrombocytopenia (platelet count < 150,000/ml), elevated serum bilirubin (> 1.1 mg/dl), hypokaliemia (serum potassium level < 3.5 mEq/L), hyponatriemia (serum sodium level < 135 mEq/L), hypoalbuminemia (albumin level < 3.5 g/dl), abnormal levels of liver enzymes (serum ALT and AST > 40 IU/L) elevated blood urea nitrogen (> 20 mg/dl), and elevated creatinine (> 1.5 mg/dl).

Treatment. All patients received artesunate-based treatment after diagnosis was confirmed by a blood smear. Based on the clinical evaluation, the application of treatment was either intravenous or orally. Two patients had received specific antimalarial treatment before admission (one patient had received one dose of chloroquine, and the other had received one dose of intravenous quinine).

Statistical analysis. Data were analyzed with SPSS version 7.5 software (SPSS Institute, Chicago, IL). The distribution of continuous variables was assessed for normality by the Kolmogorov-Smirnov test. To quantify the relationship between quantitative variables, we used, based on their distribution, either Spearman's or Pearson's correlation. Serum TNF-α levels showed a wide range of distribution and were not transformable to normality. Therefore, these parameters were analyzed by nonparametric tests. The correlations between the MODS score and FCT and PCT were adjusted for potential confounders, such as initial parasitemia and treatment regimens, by robust regression.

RESULTS

General characteristics and laboratory results. Demographic data are shown in Table 2. Twenty-two patients were admitted into the study. One patient was malnourished (body mass index < 18 and serum albumin level < 3.5 mg/dl). Sixty-

TABLE 2
General clinical and laboratory data of 22 patients with mild *Plasmodium falciparum* malaria on admission*

Parameter	Value
Age (years), mean ± SD (range)	24.8 ± 6.7 (16–41)
Males (%)	15 (68.2)
BMI, mean ± SD	20.9 ± 2.8
Previous malaria infection (%)	8 (36.4)
G6PD deficiency (%)	4 (18.2)
Duration (days) of symptoms prior to admission, mean ± SD (range)	5.3 ± 2.7 (1–10)
Temperature (°C) at blood extraction, mean ± SD (range)	37.9 ± 1.0 (36.3–39.8)
Paleness (%)	6 (27.3)
Hepatomegaly (%)	17 (77.3)
Splenomegaly (%)	5 (22.7)
Dehydration (%)	9 (40.9)
Parasitemia/μL, geometric mean (range)	10,012 (60–159,500)
Packed cell volume, mean ± SD%	34.3 ± 7.9
MCV (fL), mean ± SD	80.5 ± 10.6
WBC count/μL, mean ± SD	5.6 ± 1.4
Platelet count/mm^3 × 1,000, mean ± SD	105.5 ± 74.2
Blood urea (mg/dl), median (range)	22.1 (6.5–90)
Serum creatinine (mg/dl), mean ± SD	1.17 ± 0.24
Serum AST (IU/L), median (range)	45.5 (16–171)
Serum ALT (IU/L), mean ± SD	47.8 ± 57.3
Total bilirubin (mg/dl), mean ± SD	1.5 ± 0.9
Albumin (g/dl), mean ± SD	3.5 ± 0.67
PCT (hours), mean ± SD	49.1 ± 15.6
FCT (hours), mean ± SD	54 ± 34.9

* BMI = body mass index; G6PD = glucose-6-phosphate dehydrogenase; MCV = mean corpuscular volume; WBC = white blood cell; AST = aspartate aminotransferase; ALT = alanine aminotransferase; PCT = parasite clearance time; FCT = fever clearance time.

four percent (14 of 22) were experiencing their first malaria attack. Most (73%) of the patients received antipyretic treatment before admission. On examination at the time of admission, the mean pulse rate was 91 per minute (range = 76–120), and the mean systolic blood pressure was 115 mm of Hg (range = 90–160). Seven patients (32%) had a packed cell volume less than 30%, and six patients (28%) had a thrombocyte count less than 50,000/μL.

Serum TNF-α level. The baseline concentration of TNF-α was below the detection limit of the assay in 14 patients (64%). The remaining patients had a median serum level of 28 pg/ml (range = 10–128). This group was characterized by higher levels of serum creatinine ($P = 0.007$), blood urea ($P = 0.004$), and total bilirubin ($P = 0.03$) and lower levels of serum sodium ($P = 0.008$) and albumin ($P = 0.001$) (blood urea data analyzed by the Mann-Whitney U test, all other parameters analyzed by the *t* test). The absolute level of serum TNF-α showed a good correlation with the FCT (Spearman's r = 0.57, $P = 0.006$) and the PCT (Spearman's r = 0.48, $P = 0.02$), but not with the parasite density (Spearman's r = 0.30, $P = 0.17$). All samples of the control patients (21) had undetectable concentrations of TNF-α.

MODS in patients with uncomplicated *P. falciparum* malaria. The mean ± SD score evaluating the first 24 hours of hospitalization was 14.6 ± 2.1 (range = 11–20). Of the 10 mandatory organ systems, abnormalities were recorded most frequently in blood with a decreased hemoglobin concentration (22 of 22, 100%) and thrombocytopenia (18 of 22, 81.8%) the most common causes. Abnormalities were also observed in the central nervous system: headache (18 of 22, 81.8%) and in the gastrointestinal system: nausea (13 of 22, 59.1%), vomiting (7 of 22, 31.8%), anorexia (14 of 22, 63.6%), abdominal pain (4 of 22, 18.2%), and diarrhea (4 of 22, 18.2%). Abnormalities in metabolism were reflected by factors including hypokaliemia (5 of 22, 22.7%), hyponatriemia (10 of 22, 45.5%), hypoalbuminemia (8 of 22, 36.4%), and low levels of serum bicarbonate (5 of 22, 22.7%). Liver involvement was recorded in 14 patients (63.3%), abnormalities in the kidneys and urinary system in six patients (27.2%), elevated blood urea levels in five patients (22.7%), and increased serum creatinine levels in four patients (18.2%). Five patients had hypotension that was successfully treated with fluid replacement.

A single organ score of 3 was given to three patients in the organ system blood and to one patient with persistent hypotension in the organ system blood vessel. All of these patients had a total score of at least 15 points retrospectively. A single organ score of more than 3 was not recorded in any patient.

Relationship of MODS and TNF-α, FCT), PCT, parasite density, and clinical data. The MODS, which was evaluated within the first 24 hours, showed a strong correlation with baseline TNF-α levels (Spearman's r = 0.83, $P < 0.001$). This was still significant after adjusting for parasite density and previous antimalaria treatment ($P = 0.002$). Positive correlations were also found between the MODS and FCT, PCT, and absolute parasite count (Spearman's r = 0.58, $P = 0.005$; r = 0.54, $P = 0.009$; and r = 0.52, $P = 0.014$, respectively). After adjusting for treatment and parasite density, the correlation between MODS and both FCT and PCT remained significant ($P = 0.005$ and 0.03).

Analysis of clinical data showed a positive correlation between MODS and the duration of signs and symptoms of malaria during hospitalization (range = 1–7 days) (Spearman's r = 0.54, $P = 0.01$). This remained significant after adjusting for parasite density and treatment ($P = 0.009$). Symptoms duration that were correlated with the MODS were anorexia (14 of 22, range = 1–5 days), abdominal pain (4 of 22, range = 1–2 days), nausea (13 of 22, range = 1–3 days), and weakness (21 of 22, range = 1–7 days) (Pearson's r = 0.59, $P = 0.004$; r = 0.55, $P = 0.008$; r = 0.57, $P = 0.006$; and r = 0.46, $P = 0.03$, respectively).

The simplified MODS was also significantly correlated with baseline TNF-α levels (Spearman's r = 0.64, $P = 0.021$) and subsequent duration of symptoms (r = 0.49, $P = 0.02$), but not with FCT (r = 0.37, $P = 0.09$), parasite density (r = 0.31, $P = 0.16$), or PCT (r = 0.29, $P = 0.19$).

DISCUSSION

Using the MODS to screen a group of patients with uncomplicated *P. falciparum* malaria, we obtained different sublevels of severity. The MODS[8] on admission was highly correlated with the length of symptoms after admission and the serum level of TNF-α, which despite some technical caveats,[5] usually correlates with severity.[2–4] Using the MODS on admission, we could identify patients who were not severely ill to be classified as having severe malaria,[6] but were more ill, and for a longer time, than patients with lower scores. During malaria, an unknown proportion of the total parasite biomass is sequestered in the deep vessels, thereby hampering their normal functions. Throughout the parasite cycle, the rapidly changing dynamics of this phenomenon ultimately influence the severity of signs and symptoms. However, there is, at times, a discrepancy between the initial clinical and parasitologic assessment and the subsequent evolution. Many severity criteria reflect an illness that has already led to organ failure, but they do not account for pre-severe, i.e., early conditions. e.g., if a subcritical parasite biomass is sequestered within the organs. Attempts to predict severity by quantifying that biomass have relied on estimations from parasitologic parameters such as parasite counts, parasite staging, the presence of pigment in leukocytes,[9] or, more recently, histidine-rich protein II.[10]

This MODS cumulates equally weighted clinical and laboratory parameters that reflect the multi-system involvement seen in *P. falciparum* malaria. The cumulative nature of the score allows one to magnify dysfunctions that might not yet be clinically detectable. It is also simple and easy to apply and needs a recording time of less than three minutes.[8] A simplified MODS, based mostly on clinical parameters, might also be useful for areas with limited laboratory devices, with basic blood and urine examination as the sole laboratory facility.

Such a score could give a quantitative approach to severity, which is usually analyzed as a qualitative variable. This might be useful for researchers, who often struggle to get enough severe patients to conduct their research, and for the clinician to carefully treat patients with high scores before their conditions deteriorate to more severe disease. In this study, we used a group of patients with mild malaria to test if the score was sensitive enough to discriminate patients. However, this preliminary study has some limitations. The study population was small and did not represent the full spectrum of malaria

patients. Further studies determining the usefulness of this score should encompass all presentations of *P. falciparum* malaria to relate the score to usual criteria of severity. This could also help to calibrate a threshold useful for clinicians, and to validate the score for researchers.

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