THE USE OF THE MULTI-ORGAN-DYSFUNCTION SCORE TO DISCRIMINATE DIFFERENT LEVELS OF SEVERITY IN SEVERE AND COMPLICATED PLASMODIUM FALCIPARUM MALARIA


Clinical Department of Neurology, Innsbruck Medical University, Innsbruck, Austria; Faculty of Tropical Medicine, Mahidol University, Hospital for Tropical Diseases, Bangkok, Thailand

Abstract. Clinical presentation of Plasmodium falciparum malaria reflects a continuum from asymptomatic to multi-organ manifestation and death. Severe malaria is defined by the World Health Organization as a qualitative variable. We used the multi-organ dysfunction score (MODS) as a quantitative approach for severity in 29 patients with severe and complicated P. falciparum malaria to test its usefulness in discriminating different severity levels. The MODS on admission was highly correlated with the duration of symptoms after admission \( r = 0.73, P < 0.001 \) and the serum level of tumor necrosis factor alpha \( r = 0.41, P = 0.03 \). In addition, the simplified MODS, based mainly on clinical findings, was also correlated with liver and renal dysfunction during hospitalization (alanine transaminase, \( r = 0.42, P = 0.02 \); blood urea nitrogen, \( r = 0.45, P = 0.015 \)). A score \( \geq 16 \) was associated with significantly longer disease duration \( (P = 0.018) \). Thus, this score might provide a predicative value for morbidity in P. falciparum malaria.

INTRODUCTION

Malarial disease has a substantial social and economic impact in most tropical countries. Early diagnosis and efficacious treatment are important to reduce morbidity and mortality. Clinical presentation varies from asymptomatic to multi-organ manifestation and death, depending on host factors (e.g., immunity, age), parasite factors (e.g., plasmodia species), and the geographic location (e.g., inoculation rate).

Plasmodium falciparum is associated with both uncomplicated and severe malaria. Pathophysiologic and pathologic features of severe P. falciparum malaria include sequestration, cytoadherence, rosette formation, and reduced red blood cell deformability. Plasmodia can be found in the microvasculature of any organ of the host, which reflects the systemic nature of P. falciparum malaria. Different organ systems are usually simultaneously affected in different stages, ranging from mild dysfunction at the subclinical level to complete organ failure, triggered both by sequestration of a critical parasite biomass in small vessels and tissue hypoxia. A proper marker for severity should therefore represent the functionality of all organ-systems to find early prognostic factors to allocate more resources to severely ill patients. Existing scoring systems that reflect the multi-organ nature of P. falciparum malaria are not applicable in countries with limited resources because they are time-consuming and based on sophisticated laboratory analysis. The World Health Organization (WHO) criteria for severe malaria have been adapted for tropical regions. However, the qualitative nature (e.g., renal failure, severe anemia, pulmonary edema) may not detect pending organ failure at a subclinical level before the onset of deterioration. Furthermore, patients with single-organ failure are weighed on equal terms as those patients presenting with multi-organ failure.

Recently, we showed that the multi-organ dysfunction score (MODS), a quantitative approach for severity, was positively correlated with clinical and laboratory indices of severity in patients with uncomplicated P. falciparum malaria. A high MODS was associated with a longer duration of symptoms and signs of malaria during hospitalization. This score is widely used to assess the illness severity of patients. It was originally used in intensive care units, and is easy to apply and has a recording time of less than five minutes. In this study, our primary objectives were to identify different levels of severity in a group of patients with severe P. falciparum malaria using the MODS to compare this score with the score previously assessed in uncomplicated P. falciparum malaria patients, and to correlate this score with widely used clinical and laboratory criteria for severity, including tumor necrosis factor-\( \alpha \) (TNF-\( \alpha \)). This was chosen since parasite density in peripheral blood does not necessarily correlate with pathologic changes in each organ system.

In addition, we used the 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 Bangkok Hospital for Tropical Diseases in Bangkok, Thailand, a research hospital and referral center for tropical diseases, between October 1, 2001 and July 30, 2002.

Study population. This prospective study included 29 consecutive patients \( \geq 15 \) years of age presenting with severe P. falciparum malaria as proposed by the WHO. Diagnosis was defined by the presence of asexual forms of P. falciparum on blood smears. We excluded 1) patients with previous malaria infection in the last 30 days before admission, 2) patients known to be pregnant or lactating after childbirth, 3) patients with a proven systemic infection other than malaria, and 4) patients transferred from other hospitals already receiving specific antimalarial treatment. Additionally, for purposes of correlating the MODS with morbidity across the whole spectrum of clinical presentation of P. falciparum malaria, 22 patients with uncomplicated P. falciparum malaria previously reported were used for statistical analysis. Patients from both groups \( (n = 51) \) were prospectively enrolled during the same time period in a consecutive order. Twenty-one healthy Thai volunteers served as control for determination of the serum TNF-\( \alpha \) level.

Informed consent and ethical approval. Informed consent was obtained from all patients and control persons. For under age children, a family member or a friend responsible for them gave informed consent. The study was reviewed and
approved by the Ethical Committee of the Faculty of Tropical Medicine of Mahidol University (Bangkok, Thailand).

**Clinical and laboratory evaluation.** Study physicians, nurses, and a medical student completed a structured questionnaire and performed a physical examination. Clinical signs and symptoms were recorded daily during the first week and then weekly. Routine laboratory examinations and determination of the serum TNF-α level were performed according to a specific protocol described previously.8

**Multi-organ dysfunction score.** The illness severity of the patients was assessed by using the MODS to evaluating 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).7 The additional four optional organ systems were not evaluated in our series (skin, bone, connective tissue/endocrinology/pancreas, and peripheral nervous system). 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. The cumulative score was compared with the previously reported MODS derived from patients with uncomplicated *P. falciparum* malaria.8 Furthermore, the MODS was correlated with the duration of symptoms and signs of malaria in all consecutive admitted patients presenting with both uncomplicated and severe *P. falciparum* malaria.7

**Simplified MODS.** The simplified MODS was based on clinical parameters mostly with packed cell volume and the urine dip stick as the only laboratory support. Each organ system was evaluated by a score from one to five according to the MODS. The “heart” was evaluated by auscultation, pulse rate (temperature-adjusted, age-related), and signs of heart failure. “Blood vessel” was assessed by age-related blood pressure, the necessary therapeutic intervention (fluid challenge, specific vasoactive treatment), and circulatory collapse. “Blood” was evaluated by color, ischemic sclera, bleeding tendency due to thrombocytopenia, hyperparasitemia,8 anemia, and specific treatment (e.g., blood transfusion). Parameters for the organ system “lung” were evaluated by percussion and auscultation, i.e., age-adjusted respiration rate, signs and symptoms for mild or severe respiratory distress,6 and respiratory failure. “Metabolism” was assessed by the patients’ nutritional state, electrolyte imbalance through severe vomiting or diarrhea, Kussmaul breathing due to metabolic acidosis, and hypoalbuminemic edema. The “gastrointestinal” system was evaluated by nausea, vomiting, anorexia, diarrhea, abdominal pain. The “hepatic system” was evaluated by jaundice, liver span, and right upper quadrant pain. Dehydration, oliguria, anuria, and hemoglobinuria were parameters for evaluating the “kidney and urinary tract”, and headache, mental changes, convulsion, and the Glasgow coma scale were the criteria used for evaluating the “central nervous system.”

**Definitions.** Parasite clearance time (PCT) was defined as the duration, expressed in hours, for the parasites to decrease below the level of detection. Fever clearance time (FCT) was defined as the duration for a patients’ temperature to decrease to 37°C and remain there for at least 24 hours. Temperature was measured orally in all patients. Metabolic acidosis was defined as a plasma bicarbonate concentration < 15 mmol/L, hyperparasitemia as a peripheral parasitemia ≥ 4%,6 decreased hemoglobin (Hb) concentration as a Hb level < 14 g/dL in males and < 12 g/dL in females, thrombocytopenia as < 150,000 platelets/mL, an elevated serum bilirubin level as > 1.1 mg/dL, hypokalemia as < 3.5 mEq/L, hyponatremia as < 135 mEq/L, hypoalbuminemia as < 3.5 g/dL, abnormal liver enzyme levels as serum alanine aminotransferase and aspartate aminotransferase levels > 40 IU/L, an elevated blood urea nitrogen level as > 20 mg/dL, and an elevated creatinine level as > 1.5 mg/dL.

**Treatment.** After the diagnosis was established, all patients received intravenous artesunate at a dose of 2.4 mg/kg intravenously initially, followed by 1.2 mg/kg intravenously twice a day for the next four days, then followed by mefloquine, 25 mg/kg divided into two doses given six hours apart.10 None of the patients had received specific antimalarial treatment before admission.

**Statistical analysis.** Data were analyzed by SPSS version 11.5 software (SPSS Institute, Chicago, IL). The distribution of continuous variables was assessed for normality by using the Kolmogorov-Smirnov test. To quantify the relationship between quantitative variables, we used Spearman’s correlation. Serum TNF-α levels showed a wide range of distribution and were not transformable to normality. Therefore, these parameters were analyzed by using nonparametric tests. The correlations between the MODS and FCT and PCT were adjusted for potential confounders, such as initial parasitemia, by robust regression. The Mann-Whitney U test was used for comparing the MODS of our study population with the previously reported patients with uncomplicated malaria.8 In analyzing the symptom’s duration of all patients (uncomplicated and severe malaria patients, n = 51), we plotted Kaplan-Meier curves to compare patients with low and high MODS on admission and a log-rank test was used to test for significance.

**RESULTS**

**General characteristics and laboratory results.** Demographic data are listed in Table 1. All patients were of Thai (75.8%) or Burmese (24.1%) origin and came from the Thailand-Myanmar border area. Diagnostic criteria for severe malaria included severe respiratory distress (6 of 29, 20.7%), pulmonary edema (1 of 29, 3.4%), severe anemia (7 of 29, 24.1%), metabolic acidosis (3 of 29, 10.3%), hyperparasitemia (21 of 29, 72.4%), cerebral malaria (2 of 29, 6.9%), and acute renal failure (1 of 29, 3.4%). Fifteen patients (51.7%) had peripheral schizontemia.

Fourteen (48.3%) patients experienced their first malaria attack with a median duration of signs and symptoms before hospitalization of four days (range = 1–15 days). Most (68.9%) of the patients received antipyretic treatment before admission. Physical examination showed that four patients were malnourished (body mass index < 18 and serum albumin level < 3.5 mg/dL) with a mean systolic blood pressure of 97 mm of Hg (range = 75–130), a mean pulse rate of 105 per minute (range = 66–148), and a median respiratory rate of 28 per minute (range = 22–42).

**Serum TNF-α level.** Serum TNF-α was detectable in 14 (48.3%) patients with a median of 23.3 pg/mL (range = 10–230 pg/mL). The remaining patients had a baseline concentration below the detection limit of the assay (15 patients, 51.7%).


**Moods in patients with severe *P. falciparum* malaria.** The mean ± SD MODS evaluating the first 24 hours of hospitalization was 16.9 ± 2.6 (range = 13–25). Among the mandatory organ systems, abnormalities were recorded most frequently in the blood (29 of 29, 100%), with 12 (41.4%) patients received at least one blood transfusion, and the central nervous system (28 of 29, 96.6%), with 4 (13.8%) patients exhibiting mental changes. Abnormalities in the lung were recorded in 18 (62.1%) patients, with one patient with severe respiratory distress who needed mechanical ventilation. Twenty-eight (96.6%) patients, including 2 (6.9%) patients with severe vomiting, had gastrointestinal symptoms. Liver involvement was recorded in 20 (69%) patients, with highly elevated enzyme levels (> 3 times) in 9 (31%) patients. Abnormalities in the heart and immunology systems were observed in 2 (6.9%) patients, respectively; abnormalities of the kidneys and urinary system could be discerned in 18 (62.1%) patients, and one patient needed hemodialysis due to acute renal failure. Impaired metabolism was reflected by hypokalemia (11 of 29, 37.9%), hypoproteinemia (20 of 29, 69%), hypoalbuminemia (15 of 29, 51.7%), and low levels of serum bicarbonate (3 of 29, 10.3%), with 19 (65.5%) patients receiving specific treatment. Systolic blood pressure was low in 13 patients (44.8%) of whom five (17.2%) received specific vasoactive treatment.

A single-organ score of 4, defined as permanently decompensated organ function, was given to one patient on hemodialysis, one patient receiving mechanical ventilation, and two patients with cerebral malaria.

**Relationship of the MODS with clinical and laboratory data.** Laboratory and clinical data are listed in Tables 1 and 2. The MODS showed a strong positive correlation with the duration of signs and symptoms of malaria during hospitalization (range = 2–9 days) (Spearman’s $r = 0.73$, $P < 0.001$), which remained significant after adjusting for parasite density ($P < 0.001$). The symptoms duration that correlated with the MODS were anorexia (25 of 29, range = 0–7 days), weakness (28 of 29, range = 0–8 days), and headache (29 of 29, range = 1–6 days) (Spearman’s $r = 0.62$, $P < 0.001$; $r = 0.67$, $P < 0.001$; and $r = 0.59$, $P = 0.001$, respectively). Positive correlations were also found between the MODS and baseline TNF-α levels (Spearman’s $r = 0.41$, $P = 0.03$), FCT (Spearman’s $r = 0.49$, $P = 0.007$), and PCT (Spearman’s $r = 0.60$, $P < 0.001$), but not with parasite density ($P = 0.4$). After adjusting for parasitemia, the correlation remained significant ($P = 0.019$, $P = 0.002$, and $P < 0.001$, respectively).

**Moods in patients with severe and uncomplicated *P. falciparum* malaria (n = 51).** Patients fulfilling the severity criteria of the WHO had a significantly higher MODS on admission when compared with patients with the uncomplicated course (uncomplicated *P. falciparum* malaria: $n = 22$, mean ± SD MODS = 14.6 ± 2.1, range = 11–20) ($P = 0.002$). Correlation of the MODS with the duration of symptoms and signs during hospitalization are shown in Figure 1. A cumulative score ≥ 16 was associated with significantly longer duration of disease ($P = 0.018$, by log rank test) (Figure 2).

**Relationship of the simplified MODS with clinical and laboratory data.** Clinical and laboratory data are shown in Table 2. The simplified MODS, which is based primarily on clinical findings, was also significantly correlated with the duration of symptoms and signs of malaria during hospitalization (Spearman’s $r = 0.71$, $P < 0.001$, PCT ($r = -0.60$, $P = 0.001$), and FCT ($r = 0.41$, $P = 0.03$), but not with parasite density and baseline TNF-α level. Analysis of laboratory data showed a correlation with the lowest sodium level (Spearman’s $r = 0.60$, $P = 0.001$), highest recorded level of blood urea nitrogen (r = 0.43, $P = 0.02$), liver function parameter on day seven of hospitalization (alanine aminotransferase, $r = 0.42$, $P = 0.02$; aspartate aminotransferase, $r = 0.39$, $P = 0.03$; and conjugated bilirubin: $r = 0.47$, $P = 0.01$), as well as blood urea nitrogen on day seven after controlling for bilirubin concentration (Spearman’s $r = 0.40$, $P < 0.03$).

**Table 1**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (± SD)</td>
<td>27.1 (± 10.6)</td>
</tr>
<tr>
<td>Range</td>
<td>16–66</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>21 (72.4)</td>
</tr>
<tr>
<td>Previous malaria infection (%)</td>
<td>14 (48.3)</td>
</tr>
<tr>
<td>G6PD deficiency (%)</td>
<td>26 (89.7)</td>
</tr>
<tr>
<td>Duration of symptoms prior to admission, days (± SD)</td>
<td>4.3 (± 1.9)</td>
</tr>
<tr>
<td>Range</td>
<td>2–9</td>
</tr>
<tr>
<td>Parasitemia/μL, geometric mean (range)</td>
<td>254.84 (60–927.870)</td>
</tr>
<tr>
<td>Packed cell volume, %, mean (± SD)</td>
<td>35.9 (± 8.6)</td>
</tr>
<tr>
<td>WBCs/μL, mean (± SD)</td>
<td>6.2 (± 2.3)</td>
</tr>
<tr>
<td>Platelet count per mm³ x 1,000, mean (± SD)</td>
<td>50.93 (± 40.7)</td>
</tr>
<tr>
<td>Range</td>
<td>5–138</td>
</tr>
<tr>
<td>&lt; 20,000/μL (%)</td>
<td>7 (24.1)</td>
</tr>
<tr>
<td>Blood urea, mg/dL, median (range)</td>
<td>23.1 (11.5–101)</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL, median (range)</td>
<td>0.9 (0.6–3.1)</td>
</tr>
<tr>
<td>Serum AST, IU/L, mean (± SD)</td>
<td>79.5 (± 53.3)</td>
</tr>
<tr>
<td>Serum ALT, IU/L, mean (± SD)</td>
<td>48.5 (± 33.4)</td>
</tr>
<tr>
<td>Total bilirubin, mg/dL, median (range)</td>
<td>2.9 (0.3–20.3)</td>
</tr>
<tr>
<td>Albumin, g/dL, mean (± SD)</td>
<td>3.25 (± 0.68)</td>
</tr>
<tr>
<td>PCT, hr, mean (± SD)</td>
<td>63.2 (± 19.8)</td>
</tr>
<tr>
<td>FCT, hr, mean (± SD)</td>
<td>98.5 (± 83.6)</td>
</tr>
</tbody>
</table>

*G6PD = glucose-6-phosphate dehydrogenase; WBCs = white cells; AST = aspartate aminotransferase; ALT = alanine amino transferase; PCT = parasite clearance time; FCT = fever clearance time.*

**Table 2**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simplified MODS, mean (± SD)</td>
<td>17.2 (± 2.4)</td>
</tr>
<tr>
<td>BMI, mean (± SD)</td>
<td>20 (± 2.5)</td>
</tr>
<tr>
<td>Temperature at blood extraction (°C), mean (± SD)</td>
<td>38.3 (± 0.8)</td>
</tr>
<tr>
<td>Pulse rate per minute, mean (± SD)</td>
<td>105.6 (± 12.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm of Hg), mean (± SD)</td>
<td>97.2 (± 12.5)</td>
</tr>
</tbody>
</table>

*S MODS = multi-organ dysfunction score; BMI = body mass index.*
kine activation, hypoperfusion in the microvasculature, and tissue hypoxia. Early detection of patients at risk for developing organ failure may decrease morbidity and maybe mortality.

Using the MODS, we can express clinical presentation as a continuous variable ranging from asymptomatic to multi-organ manifestation and death. Common criteria for severe malaria describe already existing organ failure; however, a certain number of patients will deteriorate during hospitalization. Identifying the pre-severe condition as a continuous transition to severity may be useful for the clinician to allocate more resources to these patients and to the researcher to better encompass severity. Furthermore, the MODS can discriminate single-form multiple organ failure, which allows a more effective discrimination of severe presentation. A high score was associated with prolonged disease duration.

There have been several, in some aspects highly sophisticated, attempts to identify early prognostic indicators for severe malaria. In our series, we could identify a subgroup of patients with hyperparasitemia as the sole criteria for severity. Using the MODS, this group was associated with significantly shorter disease duration when compared with patients with already existing complete organ failure with or without hyperparasitemia. Hyperparasitemia was previously associated with poor prognosis and discussed in the criteria of the WHO for severe malaria; however, the presence of mature parasites in the periphery more reliably indicates severity, since parasite density in peripheral blood does not necessarily correlate with pathologic changes in each organ system. Schizontemia, which represents a high proportion of parasitized cells sequestered in the microvasculature, was found in patients with a high MODS. This may indicate a pre-severe condition or already severe organ dysfunction.

In our last series, we established the simplified MODS in uncomplicated P. falciparum malaria as a scoring system applicable for all clinics that was independent of financial resources and based on profound physical examination combined with simple laboratory analysis. This score was highly correlated with the MODS based on laboratory analysis and...
may therefore be useful for clinicians in both developing and
developed countries. The only technical devices used are a
thermometer, stethoscope, a cuff, urine dip stick, and equip-
ment for measuring packed cell volume. By using the simpli-
fied MODS, we could identify patients with prolonged renal
and hepatic dysfunction during hospitalization. Impairment
of both organ systems is a common complication in severe
malaria\(^{15,16}\) and may thus indicate a predictive value of the
MODS.

In this study, we used a group of patients afflicted by severe
and complicated malaria to examine whether the test was
sensitive enough to be used as a discriminatory analysis. Fur-
thermore, we analyzed the full spectrum of malaria patients to
find prognostic indices for poor outcome. A score \( \geq 16 \) was
associated with prolonged disease duration, which may be
useful for the clinician as a threshold. However, this prelimi-
nary study was small and did not include the spectrum of
severe manifestation sufficiently. There were only two pa-
tients who had cerebral malaria; furthermore, none of the
study patients died. Future studies representing a large popu-
lation with the full spectrum of malaria patients will deter-
dine the usefulness of this scoring method for both clinicians
and researchers.

Received May 6, 2004. Accepted for publication September 20, 2004.
Acknowledgments: We are indebted to Professor Rachane Udom-
sangpetch and Dr. Yupaporn Wattanagoon for their support, con-
tributions, and helpful critical review of the manuscript; to the nurses
of Bangkok Hospital for Tropical Diseases, whose dedication to excel-
lence in both patient care and research made this study possible, and
to all the patients who took part in this study.

Financial support: This study was supported by a grant from Mahidol
University (Bangkok, Thailand) and the Department of Neurology,
University Innsbruck (Innsbruck Austria), and by the National Insti-
tutes of Health grant ROI AI51310.

Authors’ addresses: R. Helbok, W. Dent, P. Lackner, and E.
Schmutzhard, Department of Neurology, University of Innsbruck,
Anichstrasse 35, 6020 Innsbruck, Austria. M. Nacher, S. Treeprasertsuk,
S. Krudsood, P. Wilairatana, U. Silachamroon, and S. Looaeres-
sawan, Faculty of Tropical Medicine, Hospital for Tropical Diseases,
420/6 Ratchavithi Road, 10400 Bangkok, Thailand.

Reprint requests: R. Helbok, Department of Neurology, University
of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria, Fax: 43-512-
504-4243, E-mail: raimund_helbok@yahoo.com.

REFERENCES

2. Udomsangpetch R, Chivapat S, Viriyavejakul P, Riganti M,
3. Wilairatana P, Noan NS, Chinnprasatsak S, Prodeergam K,
Kityaporn D, Looaeresawan S, 1995. Scoring systems for pre-
dicting outcomes of critically ill patients in northeastern Thai-
5. WHO. Division of Control of Tropical Diseases. 1990. Severe and
1S–65S.
assurance in intensive care medicine. Results of a multicenter
study in Germany. Anesthesiol Intensivmed Schmerzther 32:
372–375.
8. Helbok R, Dent W, Nacher M, Treeprasertsuk S, Krudsood S,
Wilairatana P, Silachamroon U, Looaeresawan S, Schmutzhard
E, 2003. Use of the multi-organ dysfunction score as a tool
to discriminate different levels of severity in uncomplicated
375.
development to prognosis in falciparum malaria. Trans R Soc Trop
10. Looaeresawan S, Waiaratanap, Mounto W, Chalermmut K, Olliaro
P, Andrial M, 1997. A comparative trial of sequential treat-
ments of severe malaria with artesunate suppository followed by
Low plasma bicarbonate predicts poor outcome of cerebral ma-
MR, Levesque MC, Mwaikambo ED, Granger DL. 2003. Low
plasma arginine concentrations in children with cerebral ma-
laria and decreased nitric oxide production. Lancet 361: 676–
678.
13. Day NP, Hien TT, Schollaartd T, Loc PP, Chuong LV, Chau TT,
Mai NT, Phu NH, Sinh DX, White NJ, Ho M, 1999. The prog-
nostic and pathophysiologic role of pro- and anti-inflammatory
14. Knisely MH, Stratman-Thomas WK, Elliot TS. 1941. Observa-
tions on circulating blood in the small vessels of internal organs
in living Macaca rhesus infected with malaria parasites. Anat
Rec 79: 90.
Ren Fail 12: 15–19.
16. Trang TT, Phu NH, Vinh H, Hien TT, Cuong BM Chau TT, Mai
17. Wilairatana P, Looaeresawan S, Charoenlarp P. 1989. Liver pro-
file changes and complications in jaundiced patients with fal-